United States
Environmental Protection
Agency

Office of the Administrator
Science Advisory Board (A-101)
401 M Street, SW
Washington, DC 20460

October 1986

EPA

Review of 37 Office of Drinking Water Health Advisories by the Environmental Health Committee of The Science Advisory Board

- Metals Subcommittee: (SAB-EHC-87-004)

  arsenic, barium, cadmium, chromium, cyanide, lead, mercury, nickel, and nitrate/nitrite

- Halogenated Organics Subcommittee: (SAB-EHC-87-005)

  carbon tetrachloride, chlorobenzene, dichlorobenzene, 1,2-dichloroethylene, cis and trans 1,2-dichloroethylene, 1,1-dichloroethylene, epichlorohydrin, hexachlorobenzene, polychlorinated biphenyls, tetrachloroethylene, 1,1,2-trichloroethylene, 1,1,1,-trichloroethylene, and vinyl chloride.

- Drinking Water Subcommittee: (SAB-EHC-87-006)

  acylamide, benzene, p-dioxane, ethylbenzene, ethylene glycol, hexane, Legionella, methylethylketone, styrene, toluene, and xylene

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C. 20460

October 24, 1986

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Environmental Health Committee of EPA's Science Advisory Board has completed its review, requested by the Office of Drinking Water (ODW), of thirty-seven drinking water health advisories. The Committee accomplished this task by assigning the review to three separate subcommittees: Metals, Halogenated Organics and Drinking Water. The Science Advisory Board has not previously reviewed health advisories, and its participation in this program has been informative.

The Agency's development of health advisories represents an important component of its drinking water program. By seeking to improve their scientific quality, EPA will better serve the needs of state and local officials who have a legitimate need for the advisories.

In order not to delay the ODW's revision of the advisories, the three subcommittees have already provided transcripts of their oral comments and about 110 pages of detailed comments. The final comments are enclosed with this letter as three Subcommittee reports. The major conclusions of the review are as follows:

- The Subcommittees found the health advisories uneven with respect to their scientific quality. The Office of Drinking Water should develop guidance to assure more consistent quality in the future.

- The Office of Drinking Water has made a commendable effort to provide exposure analysis information in the draft health advisories, including the consideration of exposure from drinking water through routes other than oral ingestion, and the utilization of inhalation toxicologic data. The Subcommittees encourage ODW to perform even more of this work.

- The major problem in reviewing the health advisories was to understand the draft documents in relation to their intended audience(s). According to the Office of Drinking Water, there are multiple audiences with different skill and background levels, such as operating personnel of waterworks and public health officials. As

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currently written, the health advisories have the appropriate format and content to satisfy the needs of persons with expertise in toxicology, such as health officials, but not operating personnel. Therefore, the Subcommittees advise that the health advisories not provide summary numerical tables, as indicated in the current drafts. Instead, they recommend that each health advisory contain a narrative summary, written in a style that can be understood by lay persons.

- There will be less of a problem with communicating with various audiences if the Office of Drinking Water adopts a three step process to document drinking water contaminants. This process includes developing Criteria Documents to support Agency regulations; preparing health advisories for public health authorities; and writing a narrative summary for operating personnel of waterworks. The major role for the Science Advisory Board within this process will be to review Criteria Documents and selected health advisories.

The Science Advisory Board appreciates the opportunity to review the health advisories. In behalf of the Board, we request that the Agency formally respond to the scientific advice contained in the attached reports.

Sincerely,

Richard Griesemer

Richard Griesemer
Chairman, Environmental Health Committee
Science Advisory Board

Norton Nelson

Norton Nelson
Chairman, Executive Committee

United States
Environmental Protection
Agency

Office of the Administrator
Science Advisory Board (A-101)
401 M Street, SW
Washington, DC 20460

SAB-EHC-87-004
October 1986

EPA

Review of Drinking Water Health Advisories by the Metals Subcommittee of The Environmental Health Committee of The Science Advisory Board

- Arsenic
- Barium
- Cadmium
- Chromium
- Cyanide
- Lead
- Mercury
- Nickel
- Nitrate and Nitrite

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

September 20, 1986 SAB-EHC-87-004

OFFICE OF
THE ADMINISTRATOR

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board [A-101]
U.S. Environmental Protection Agency
401 M Street, SW
Wasington, DC 20460

Dear Dr. Griesemer:

On January 9-10, 1986 the Metals Subcommittee of the Enviropmental Health Committee reviewed nine (9) draft health advisories for drinking water in public session. The draft health advisories were prepared by the Office of Drinking Water. The health advisories are not regulatory documents but are intended to provide consistent, brief reference information, particularly for technical personnel responsible for the operation of water works or for state and local public health officials. During the review of the health advisories, the Subcommittee utilized Drinking Water Criteria Documents for these substances as support documents. The Subcommittee recommends that the Criteria Document for Mercury undergo further detailed scientific review, because this is the first attempt to set forth the Agency's evaluation of ionic mercury, and some scientific issues will be controversial.

Our comments below are divided into general advice, which is relevant to all of the advisories reviewed by the Subcommittee, followed by advice specific to each of the substances reviewed. Based on the general review, the Subcommittee recommends that the Office of Drinking Water undertake an updating of three guidance documents (issue papers) for use of inhalation data, pharmacokinetics and multiple exposures (mixtures). Although the guidance may be conceptually sound for organic substances, some information in the documents seems inappropriate to the toxicology of metals. Because of the extensive nature of our comments, a Table of Contents and some supporting appendices are included. We appreciate the opportunity to become involved with this program and stand ready to provide further advice, as requested.

Sincerely,

Bernard Weiss

Bernard Weiss, Ph.D.
Chair, Metals Subcommittee

Ronald Wyzga

Ronald Wyzga, Sc.D.
Vice-chair, Metals Subcommittee

EPA NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency, and hence the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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I. GENERAL COMMENTS OF THE METALS SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA'S SCIENCE ADVISORY BOARD REGARDING DRINKING WATER HEALTH ADVISORIES

A. THE RELATIONSHIP BETWEEN AUDIENCE AND CONTENT NEEDS CLARIFICATION.

The format and content of the health advisories are inconsistent with the audience for which they are intended. Often the descriptions of studies bear only a remote relationship to the aims of the health advisories. Lethal doses in animals, or details of pathological surveys in rodents after high doses, for example, are not usually necessary to convey the basis for the "risk reference dose." A related problem with the health advisories is the presentation of the information. Typically, a few papers are tersely abstracted, with little attempt to integrate their contents. The nickel health advisory, for example, lists nine studies under the heading, "longer-term exposure." Two pages later, under the heading "longer-term health advisory," it states that no suitable studies were identified to derive the longer-term health advisory. Not only were the nine studies not pertinent, but they were described as if in an annotated bibliography, lacking any attempt to integrate their findings. The health advisories should be made crisper and clearer and feature only those data upon which the various calculations rely.

B. THE HEALTH ADVISORIES HAVE DIFFERENT UNCERTAINTIES.

Various health advisories have different degrees of uncertainty associated with them. The uncertainty results from one or more of the following:

- No adequate data exist which can be used to derive a health advisory. The health advisory for arsenic, for example, is based upon subjective opinions about the best experimental data to use.

- A health advisory is calculated from animal data, and it is unclear how to extrapolate to humans. See, for example, the chromium health advisory.

- Health effects data exist for another route of exposure, and it is unclear how and whether to extrapolate for exposure via another media. For example, chromium (VI) is a reasonably well-established carcinogen associated with respiratory cancers, yet the health advisory for chromium states that there is inadequate evidence to determine whether or not oral exposure to chromium can lead to cancer. In such situations, it is unclear whether and how inhalation effects data can be used for health advisories. A different example occurs in the derivation of the lifetime health advisory for mercury. Effects following subcutaneous injection were used to estimate effects from drinking water exposure.

- Exposure durations are different for the health advisory and for the study used to derive the advisory. For example, a 24-week study was used to derive the 10-day health advisory for cadmium.

- There is thought to be some difference in the toxicity of alternative species of a metal, but species-specific health advisories are not estimated. Arsenic is an example here, where the trivalent species is believed to be most toxic, but insufficient data exist to derive species-specific health advisories.

• Different sensitivities were likely applied to alternative studies in measuring health effects. For example, the ten-day health advisory for chromium is based upon an increased incidence of "slight roughness of coat." Other endpoints appear to reflect more severe response.

• There may be conflicting information between two or more studies. For example, the lifetime health advisory for mercury would differ by several hundred fold if an alternative study were used to calculate it. Conflicting studies may have different scientific merit. For example, one study may not have a control group and another may have an incorrect statistical analysis. There is considerable uncertainty in exactly how one should weigh the different merits of these studies.

• A health advisory may be highly dependent on the design of the experiment used to estimate the advisory. For example, the lifetime health advisory for cyanide is based upon a study undertaken at two dose levels. No effects were found at either level, hence, the higher level is assumed to be the no--observed-effect-level. If alternative dose levels were chosen for this experiment, it is likely that both the no-observed-effect-level and the health advisory would differ from the current values.

• The experimental design will also influence the power or ability of an experiment to detect a statistically significant health response from increased exposure to a toxic substance.

• Doses in certain experiments were administered in media other than water. If absorption varies by media, this will produce uncertainty for developing advisories. For example, the lifetime health advisory for nickel is based upon a study of nickel administered through milk.

• The health risk depends on other sources of the metal, and these will vary.

• Interactions may occur between the substance of concern in the drinking water and other substances.

• A lack of understanding of the underlying biological mechanism can impede the interpretation of experimental results.

• The toxicologically critical organ and the critical effect are useful concepts that need to be differentiated, or an uncertainty will be created. The critical organ is the main target of a particular toxicant. The critical effect is the earliest adverse effect to appear. For cadmium, the kidney is the critical organ, whereas many toxicologists believe that beta-2-microglobulinemia is the critical effect. The health advisories should recognize this distinction explicitly and address each accordingly.

To adjust for uncertainty, the health advisories usually reflect assumptions designed to err on the side of safety, and they utilize safety factors in order to be protective of public health. The use of (and rationale for) bias in the interpretation of assumptions and safety factors needs to be clearly explained in the health advisories, in order for them to meet their stated purpose of providing useful information in the field. Without some indication of the bias, operating personnel cannot distinguish between a

decrease in the margin of safety and the imminent possibility of mortality or morbidity in the consuming population. It would be useful, moreover, to provide some indication of the uncertainty associated with a health advisory. The simplest way to do this would be to indicate explicitly the nature of the uncertainties. These could be taken, for example, from the above list. Alternatively, the Agency could develop and incorporate a system to express the levels of confidence associated with the health advisory. Such a system has recently been incorporated into EPA's risk assessment guidelines for mixtures.

C. BIOPROCESSING OF THE METALS NEEDS A CLEARER PRESENTATION.

The Subcommittee noted some inconsistencies in the pharmacokinetics sections between different health advisories for metals and inorganic substances. The content and depth of the discussions varied considerably. In some advisories, extensive animal data were presented without adequate interpretation (e.g., absorption of chromium), and in other places general interpretive statements were presented without data (e.g., absorption of barium). Also, there appeared to be inconsistencies in the definition of the various components of the bioprocessing of metals (absorption, distribution, metabolism and excretion). Examples of this include the following:

- Binding of chromium to iron-binding proteins is discussed in the section on distribution, whereas binding of cadmium to metallothionein is discussed in the section on metabolism.

- Retention of cadmium is discussed in the section on absorption rather than in the section on excretion.

- Renal processing of chromium is discussed in the section on distribution rather than in the section on excretion.

- Transport of chromium is discussed in the section on metabolism rather than the section on distribution.

- Retention of lead is discussed in the section on metabolism.

- The transfer of lead across the placenta is discussed in the section on metabolism rather than in the section on distribution.

- The transfer of nickel across the placenta is discussed in the section on metabolism rather than in the section on distribution.

Inconsistencies such as those cited above confuse the reader, making it difficult to abstract information from the documents and reducing confidence in the documents. It would be helpful if a uniform set of definitions of each of these processes was adopted, and if information concerning each process was categorized in the document accordingly. Also, statements in the documents should be interpretive and should focus on the bioprocessing of metals in humans. If this involves extrapolation from laboratory animal data, the extrapolation should be indicated.

The Subcommittee proposes the following suggestions for the content of the various subsections of the pharmacokinetics sections of the health advisories:

- "Absorption" refers to the processes by which metals enter the internal environment of the body. In this section all routes of absorption that are relevant to human exposure should be indicated, including inhalation of volatile materials from drinking water sources and so forth. Factors that influence the magnitude of gastrointestinal absorption should be indicated. A quantitative estimate of the percent absorption from the gastrointestinal tract in humans (or a range of values) should be provided. The source of the data from which the estimate was made should be indicated (e.g. human data, laboratory animal experiments or conjecture).

- The "distribution" section should describe where the metal is located in the human body. If human data is not available, the location may be inferred through data from laboratory animals or from analogy to similar substances. If possible, a quantitative description should be provided of the distribution of the body burden. This description should indicate the largest depots for the metal and the target tissues. Factors that influence the distribution should be indicated (e.g., speciation, route of absorption or other substances). Transfer of metals across the placenta to the fetus should be discussed in this section. Mechanisms of entry of the metal into target tissues (e.g. membrane transport), if discussed at all, should be reviewed in this section.

- The "metabolism" section should describe the chemical conversions of the metal that are relevant to the absorption, distribution, excretion, detoxification and activation of the metal. This includes oxidation or reduction reactions, binding to intracellular or extracellular proteins, and chelation or complex formation with inorganic components of bone. The significance of metabolism to the overall distribution and elimination of the metal and to the toxicity of the metal should be discussed.

- Under "excretion," a description of the elimination kinetics (e.g., biological half-life) should be presented in each health advisory. The routes of excretion should be identified, and the relative contributions of each of the routes should be discussed. In discussing the fecal excretion of metals, it is important to distinguish the excretion of ingested and nonabsorbed metal from the excretion of absorbed metal. Mechanisms of excretion (e.g., renal tubular transport), if discussed at all, should be reviewed in this section.

D. BIOLOGICAL EFFECTS VARY WITH SPECIATION OF METALS.

In general, metals exist in a number of physical and chemical species. Changes in oxidation state and the formation of organo-metallic compounds (where the metal is covalently bound to at least one carbon atom) are forms of speciation that may have a profound influence on the toxicity of the metal. Speciation should be considered in most of the sub-sections of the health advisory.

In the "occurrence" sections, the global cycle of the metal frequently involves interconversion to more soluble or more volatile species of the metal. The methylation of inorganic mercury in freshwater and oceanic sediments is a key step to the bioaccumulation of mercury in aquatic food chains. The redox potential in water supplies may influence the species in drinking water. The oxidation of trivalent to pentavalent arsenic occurs in well oxygenated water supplies.

In the pharmacokinetics sections, essentially the same principles as above will explain the importance of species in the uptake, distribution, metabolism and excretion of metals. Trivalent chromium crosses cell membranes much more slowly than hexavalent chromium. The methylated forms of metals usually are absorbed better than the inorganic species. Methylmercury must first be demethylated before excretion can take place.

Metallic cations can form a wide variety of complexes with ligands in cells and biological fluids. The induction of and binding to metallothionein by cadmium explains the long-term accumulation of the metals in the kidney. The formation of a glutathione complex in the liver is a key step in the biliary excretion of mercury. The failure to secrete biliary glutathione explains the lack of fecal excretion of mercury in suckling animals.

In the health effects sections, speciation will influence the occurence of health effects both by affecting the pharmacokinetics of the metal or by changing the chemical reactivity and cellular toxicity of the metal. Trivalent arsenic binds to neighboring sulphydryl groups inhibiting sulphydryl containing enzymes and co-factors, such as lipoic acid. Pentavalent arsenic, in the form of anionic arsenates, follows the same metabolic pathway as phosphates, causing uncoupling of high energy phosphate synthesis. Organic metallic compounds such as methylmercury, tetramethyl lead and tetramethyltin produce much more serious effects on the brain than their inorganic counterparts. Carcinogenic properties are well-established for nickel subsulfide but not for soluble nickel compounds.

In the quantification of toxicological effects sections, speciation becomes an important consideration in assessing the importance of different routes of intake to total exposure to the metal and to decisions on using toxicological data from experiments with different routes of exposure. Inhalation studies indicating the carcinogenic effects of nickel subsulfide in lung tissues are probably not relevant to dietary uptake of nickel that will be present in food as a different chemical species. On the other hand, studies on inhaled cadmium compounds may be relevant to dietary intake, if kidney effects are the endpoint for both routes. The same species of cadmium (inorganic divalent cadmium) is involved in renal uptake. The relative contribution of air, water and food to total lead uptake can be directly compared as inorganic lead is the common species. This is not the case with mercury. Mercury vapor is the predominant species in air, methylmercury in food and inorganic divalent mercury in drinking water. Mercury vapor in air and inorganic mercury in food may be compared, if kidney damage is the endpoint. None of these species are comparable if nerve damage is the health effect of concern.

E. MULTIPLE SOURCES OF EXPOSURE INFLUENCE THE HEALTH ADVISORIES.

For most metals, the normal route of intake involves several sources whose relative contributions differ. Often, food constitutes the predominant source and this should obviously be taken into consideration when calculating the health advisory, and it has been practiced in the present set of health advisories. However, it is not clear how the values for source contributions (X% food, 100-X% water) were derived, and this should be stated for the individual metal. In most cases, the source contribution factor may just be a crude speculation, but even such conjectures usually have some basis.

A more serious concern arises when a major contribution and route of exposure is via inhalation. This is of particular importance (a) when the target organ is the respiratory tract and the chemical accumulates in or affects the lung after it is absorbed from the gastrointestinal tract; or (b) when there is a well-defined target organ which is different from the lung where the chemical accumulates once it is absorbed into the blood circulation from either lung or gastrointestinal tract.

Case (a) might be a more hypothetical one, but for case (b) several examples can be given. Lead from automobile exhaust accumulates in the central nervous system; mercury vapor released from dental fillings accumulates as divalent mercuric ion in the kidney; and cadmium inhaled by cigarette smoking accumulates in the kidney. In those cases, where the contribution from inhalation can approach a significant or even major portion of the daily intake, inhalation data must be taken into account and the health advisory must be adjusted accordingly. This has to be evaluated for each chemical individually and is exemplified further in the specific comments for cadmium in this report.

The percentage of the population affected by additional inhalational intake should be considered in a health advisory. For example, if only a small percentage (less than 2%) of the population is exposed occupationally by inhalation to a chemical, such that a major portion of the body burden of the chemical is derived from this occupational activity, should this be reflected in the health advisory? (Examples are workers exposed to manganese dust, mercury vapor or cadmium aerosols in the workplace.) From a scientific point-of-view, both occupational and environmental standards should consider total exposure, unless the applied safety factor in the calculation of the health advisory convincingly covers the additional intake by occupational exposure (or the occupational standard covers environmental exposure). This should then be stated.

If the percentage of people with inhalational exposure is significant, this additional intake will affect the calcualtions in a health advisory. One example, the impact on the cadmium health advisory of smokers in the U.S. population, is described in the specific comments section. In summmary, cigarette smoking alone can contribute as much or more than the daily recommended dose that EPA estimates for non-smokers. Perhaps the applied safety factor of 10 in the present health advisory is high enough to protect smokers also. Nevertheless, a discussion about these relationships should be included in the health advisory.

In any event, multiple exposure sources have to be taken into account once it becomes obvious from knowledge of the pharmacokinetics of a chemical

that lung absorption can significantly contribute to a target site dose. Local authorities should be alerted to the fact that occupational exposure can significantly add to the body burden. Possibly, a "secondary" health advisory can be established for those situations taking into account occupational exposure. With this knowledge and information, local authorities will be able to decide where to set their drinking water standard.

F. HEALTH ADVISORIES SHOULD DESCRIBE THE RELATIVE CONTRIBUTION OF DRINKING WATER TO EXPOSURE.

For each metal, the Subcommittee suggests that a table (or summary statement) be inserted into the health advisory detailing the relative (intake) contributions for humans from different sources, including water. The importance of this table is described in the specific comments for the lead health advisory. An example of a table is given below for lead. EPA also should consider adding an additional column which indicates "percent absorbed." The resulting figure would represent a net contribution which may mean more to the reader than quantity of source. For example, lung absorption for lead is about one hundred percent for the appropriate particle size; for cadmium, it can be close to one hundred percent, whereas gastrointestinal tract absorption is ten to fifteen percent for both metals. Lead absorption is higher in infants, but there is no infant data for cadmium.

Human Lead Exposure*

	2-year-old child		Adult male	
Source	ug/day	Total (%)	ug/day	Total (%)
Air	0.5	1	1.0	2
Food	18.9	40	35.8	59
Dust	21.0	44	4.5	8
Water	6.9	15	18.9	31
Total	47.3	100	60.2	100

* Adapted from support documents for the lead health advisory.

II. SPECIFIC COMMENTS OF THE METALS SUBCOMMITTEE ABOUT THE HEALTH ADVISORIES FOR METALS AND ASSOCIATED SUBSTANCES

A. ARSENIC HEALTH ADVISORY

The health advisory for arsenic reasonably summarizes the pertinent information available in the Criteria Document. Except for carcinogenic effects, much of the available information on the toxicity of arsenic is anecdotal and/or of limited value in calculating a health advisory. Animal experiments were carried out at very high dose levels. Given the uncertainty about how to extrapolate the outcome of these studies to humans at ambient level arsenic concentrations, animal experiments could not be used to calculate the health advisory values.

It was not possible to apply the formula in the section on quantification of toxicological effects, or any other quantitative method, to derive health advisory values. The result is the adoption of a National Academy of Sciences recommendation. Therefore, more detail should be given to indicate the rationale for this National Academy of Sciences recommendation. In any case, there is considerable uncertainty associated with the health advisory, and this should be specifically indicated. Given the statements that data or evidence exist which indicate that some species of arsenic are more toxic than others, the Office of Drinking Water should consider the possibility of a health advisory specific for an ionic species. Using different assumptions, such as the human essentiality of arsenic, alternative estimates could have been calculated.

The health advisory should be placed in perspective. Assuming an adult drinks 2 liters of water a day, the total consumption of arsenic is about 0.1 mg/day at the health advisory concentration. This level of ingestion should be contrasted with the oral intake of arsenic from diet and other sources.

Two different formulae are given for sodium arsenite. The second should be sodium arsenate.

In the health effects section, the health advisory notes that the toxicity of arsenic depends on its chemical form, yet the summary of health effects information does not support this statement, implying that some relevant information is not mentioned. Descriptions of the animal studies include material on As^{+5} that hardly seem worthwhile given the statements that the toxic species is As^{+3}. The studies which support the conclusions about species-specific toxicity in this section should be cited. A slightly expanded summary in the health effects section would result in a better investment of the reader's time.

The Criteria Document raises questions about the Zaldevar study in the longer-term exposure section. For example, it notes that "the decrease in cutaneous lesions seemed to be too rapid following installation of the water-treatment plant". Accordingly, some qualification should be given to this study in the health advisory, noting that the decrease of some symptoms seemed to be too dramatic as arsenic concentrations decreased to 0.08 mg/L.

The health advisory should mention that the study of Tseng and coworkers has been heavily criticized because of the presence of confounding factors in the study population. The Office of Drinking Water also should note the comments of Andelman and Barnett in the article cited in the health advisory. Many of the U.S. studies may have been negative because of the small size of the study populations and their correspondingly low power to detect a significant increase in health effects.

It is ironic that the same advisory value is calculated for short-term and long term exposure given the statement that toxicity is duration-dependent.

The review of carcinogenicity omits human data from Argentina.

B. BARIUM HEALTH ADVISORY

The arguments for determining the uncertainty factors for barium are not convincing. Why was the uncertainty factor dropped from 1000 to 100? How was a factor of 10 derived as a quantitative measure of the effects of the defined diet on hypertension? There is no critical evaluation of the calculated lifetime health advisory (for example, possible sources of error, subpopulations to which the calculated health advisory may not apply, and information that is unavailable but critical to improving the calculation). Should not a factor similar to the one for defined diet be included that quantifies differences in gastrointestinal absorption of barium in young animals?

The document states that there were no signs of toxicity at any barium dose level. This statement is not correct since hypertension was evident in rats given 100 ppm barium in the study of Perry and coworkers. Indeed, the hypertensive effects of barium are used to calculate the lifetime health advisory. Although, in the lifetime health advisory, an increase in blood pressure of 4 to 7 mm (Hg) was not large enough to be considered an adverse effect, elevations of this magnitude traced to lead exposure are considered by EPA to be a significant public health problem. The evaluation of the study by Tardiff and coworkers concludes that no conclusive signs of barium toxicity were observed. This evaluation should be reconsidered since blood pressure was not measured in this study. Perhaps the evaluation should state that there were no additional signs of toxicity at any dose of barium.

It is not clear why the lowest-observed-adverse-effect-level was established as 5.1 mg/kg.day rather than 0.51 mg/kg·day. The study by Perry and coworkers demonstrated significant elevation of blood pressure in rats given 0.51 mg Ba/kg·day for 8 months. In the same study, hypertension was evident in rats given 5.1 mg Ba/kg.day for only 1 month. Thus, the results of this study support a lowest-observed-adverse-effect-level that may be as low as 0.51 Ba mg/kg·day.

EPA reported several other changes in rats given 100 ppm barium that could be considered as evidence of barium-induced toxicity, such as decreased content of adenosine triphosphate and phosphocreatinine in myocardium, decreased rates of cardiac contraction and depressed electrical activity of the myocardium. In the study by Schroeder and Mitchener, increased proteinuria was observed in rats exposed to approximately 0.25 mg Ba/kg·day for 173 days. The acute toxic threshold dose that is cited in the Criteria Document is 2.9 to 71 mg/kg, whereas the health advisory cites a value of 2.9 to 7.1 mg/kg. Which value is correct?

Citations of scientific literature to support certain statements in the document are missing. Literature citations to support statements concerning the solubility of barium compounds in water and the effects of pH on solubility should be provided. Literature citations to support statements concerning the natural abundance of barium compounds, sources of contamination of drinking water and levels of barium in drinking water should be provided.

The information provided in the document ranges from detailed and highly

technical to vague. Similarly, the document will be improved by using consistent units to describe barium concentration.

The sections about pharmacokinetics were difficult for the Subcommittee to understand. It is not clear what is meant by the statement that substitution of barium for strontium and potassium ions is common. The metabolism of barium should be described in greater detail, particularly the incorporation of barium into bone. Statements concerning the similarities between the skeletal metabolism of barium and calcium do not summarize the skeletal metabolism of calcium and provide useful information only to those individuals who are knowledgeable about calcium. While data obtained from studies of laboratory animals by Lengemann suggest that barium absorption in young animals may be significantly greater than in adult animals, information is currently inadequate to determine if this applies to humans. Only the mouse data is analyzed in the distribution section. This section should summarize the human autopsy data and the data on retention of barium in humans that is presented in the Criteria Document.

Information about the relative magnitudes of fecal and urinary excretion could be presented. The role of diet is discussed too tersely and is confusing. No mention is made of the magnitude of excretion of barium in maternal milk. The Criteria Document reports that 10% of an intravenously administered dose of barium is excreted in the milk of lactating cows. If this applies to humans, excretion of absorbed barium in maternal milk could be a more significant excretory route in lactating females than is excretion in urine.

C. CADMIUM HEALTH ADVISORY

The data base for cadmium appears to be fairly complete, although information on cadmium intake via smoking is missing. The acceptable daily intake calculations seem to be correct. However, the ten day advisory is based on values from a study of 24 week duration. The calculations for the longer-term health advisory of 18 ug/L value are not given. How is it derived? The basis for the uncertainty factor of ten, rather the more ususal value of one hundred, should be explained. A rationale exists in the narrow, measurable range of cumulative doses that cause renal disease. There is no critical evaluation in the health advisory of possible sources of error, subpopulations to which the calculations may not apply or information that is unavailable but critical for improving the calculation. The dose of cadmium might be expressed per kg body to facilitate comparisons with other data in the text. The basis for using 10 kg or 70 kg for body weight in the calculation of health advisory should be explained. Similarly, the calculation of the longer-term health advisory for a child of 5 ug/L is not explained.

The risk reference dose (RRFD) of 35 ug/d approximately equals the current U.S. daily intake of cadmium from all sources (mostly food). Using conservative assumptions, the Friberg model yields 352 ug/d as the minimum daily dose that would result in an adverse effect (renal tubular dysfunction). No need exists for an additional safety or uncertainty factor because these data arise from the most sensitive human subpopulation. Many scientists believe that a risk reference dose of about 200 ug/d is adequate protection for humans. The World Health Organization and the European Economic Community have set their standards at this level. However, if EPA retains the current risk reference dose, the Agency should communicate it to the U.S. Food and Drug Administration and the Department of Agriculture, as changes in the pattern of food consumption will be required.

The general question of including effects of widely practiced social habits should be addressed. Specifically, the intake of toxicants by cigarette smoking should be considered. For example, the health advisory is based on the assumption that the risk reference dose is 0.5 ug cadmium per kg·day or 35 ug/day for a 70 kg man. The statement that food appears to be the major route of exposure for cadmium should be modified for smokers. Cigarette smokers constitute approximately 30% of the population, and they will take in an additional amount equal to or exceeding the dietary intake. The health advisory assumes that drinking water contributes 25% of total cadmium intake with the remainder derived from food, which gives a lifetime health advisory of 5 ug/L. It is not entirely clear how the contribution from smoking will affect this calculation, but perhaps it will be lower by a factor of two.

The effects of other metals affecting cadmium absorption should be mentioned, particularly zinc. Lung absorption is not described, although it is important and is discussed in the Criteria Document, and absorption calculations will be in error if this contribution is not included. The main reason for the long half-time of cadmium in the body should be described, i.e., retention in the kidney. Statements about the retention of radiolabelled cadmium chloride do not belong in the absorption subsection. In the study by McLellan and coworkers, the retention of orally administered cadmium was used to

estimate the gastrointestinal absorption of cadmium, but the statement in the advisory about this study does not indicate what was learned about absorption from the study. Perhaps the results of the studies of gastrointestinal absorption of cadmium in humans and studies of laboratory animals that are described in the Criteria Document should be summarized. The statement that cadmium does not cross the skin is vague. Can a quantitative expression be used to describe the absorption of cadmium across the skin? Is data available on the absorption of cadmium across skin in humans?

The whole section on health effects should be reorganized to present a clearer summary, with a emphasis on the kidney as a target organ, rather than a loosely linked series of annotated references. The health effects of cadmium occur as a sequence of events, in which beta-2-microglobulinemia is an earlier indicator. The reference to Itai-Itai disease should note that it appeared in elderly, multiparous women. This disease may not be a sole consequence of high levels of cadmium exposure. Instead, cadmium may be an etiological factor. The symptoms described for humans are for oral exposure. Similarly, for animal data, it is not clear whether described effects are for oral exposure or also after other routes of cadmium administration (injection). If the latter is the case, inhalation effects also ought to be included. The epidemiology study by Thun and coworkers should be cited in the subsection about humans. A better explanation should be provided to support the statement that data on cadmium carcinogenicity are not thought relevant to the consumption of cadmium in drinking water. Effects of cadmium on the respiratory system are not discussed or recognized as human health concerns in the health advisory. This may mislead readers who are not knowledgeable about these aspects of cadmium toxicology.

Friberg and coworkers estimated the daily intake of cadmium that would result in the accumulation of 200 ug cadmium/g renal cortical tissue after 50 years of continuous exposure. Roels and coworkers have shown that this level of cadmium occurs in human kidneys that exhibit symptoms of renal impairment. The health advisory should summarize this information.

Testes exhibit toxic effects after parenteral administration of cadmium. The Subcommittee is divided on the importance of this phenomenon. The results do show that testes of the rat are a sensitive organ for cadmium. However, the pathological effects occur only after massive parenteral doses and after necrosis in blood vessels leading to the testes. Thus, these observations do not have public health significance.

Since the Threshold Limit Values established by the American Conference of Governmental Industrial Hygienists are given, the Occupational Safety and Health Administration's workplace exposure limits should also be described, since these are the legally binding limits for cadmium as dust (0.2 mg/m^3) or fume (0.1 mg/m^3).

What is the evidence to support the statement that commercial use of cadmium has not resulted in the contamination of ground and surface waters? Does this mean that all cadmium in ground and surface water (1-10 ug cadmium/L) is derived from natural sources?

D. CHROMIUM HEALTH ADVISORY

Most of the health advisory evaluation of chromium is accurate, complete and in agreement with the Criteria Document. However, the section on health effects does not adequately reflect the body of the evidence presented in the Criteria Document and is open to question on the evaluation of both carcinogenic and non-carcinogenic effects.

Both the Criteria Document and the health advisory make efforts to distinguish between chromium (III) and chromium (VI). This distinction is important as the toxicity of chromium has been attributed primarily to chromium (VI). The main difficulty with this advisory concerns the appraisal of the carcinogenicity of chromium (VI). The health advisory states that there is inadequate evidence to determine whether or not oral exposure to chromium can lead to cancer. While this is true, there is strong evidence that inhalation of chromium (VI) increases the risk of cancer (most notably for the lung), although there is no direct evidence of carcinogenicity from oral exposure. The advisory concludes that the carcinogenicity of inhaled chromium (VI) has no bearing on risk following oral exposure. This statement is not well justified.

The Criteria Document notes that the International Agency for Research on Cancer concluded that chromium falls into its Group 1 category (meaning that sufficient evidence exists to demonstrate that the chemical is carcinogenic in humans). However, this categorization was not included in the advisory. Further, EPA's Health Assessment Document for Chromium reviews this evidence and reaches agreement with the International Agency for Research on Cancer's categorization. Although the categorization results primarily from inhalation data, it seems reasonable to include it in the advisory (with the associated caveats on inhalational versus oral data). There is one animal study on ingestion of chromium by Ivankovic and Preussman, but it involved chromium (III) not chromium (VI).

The Criteria Document does not attempt to reach either a qualitative or quantitative conclusion on the carcinogenic risk from oral exposure through drinking water based on the inhalation data. Nevertheless, it is critical to consider the carcinogenicity of chromium (VI) from oral exposure in light of the inhalation data, the pharmacokinetics, metabolism and mutagenic effects of chromium (VI). A supporting issue paper reviews the use of inhalation data to develop acceptable exposure levels in drinking water and, therefore, a policy basis exists for the Office of Drinking Water to make this extrapolation for the sake of consistency. However, the Metals Subcommittee recommends that the Office of Drinking Water not use this exact method, since this issue paper is in need of revision.

A secondary concern involves the assessment of the noncarcinogenic health effects in humans. In presenting the evidence, the advisory gives strong weight to a report on the effect of drinking water containing 1 mg/L of chromium (VI) in one family of four persons, based on a physical exam. This report is anecodotal and has little scientific value. Neither was a control family studied nor were details given on health effects measured. In contrast, the health advisory notes that chronic inhalation of dust or air containing chromium (VI) may cause respiratory problems. However, these risks seem understated as the Criteria Document describes at least three well designed and

controlled epidemiologic studies which conclude that chronic inhalation of air containing chromium (VI) causes respiratory problems.

Animal studies on non-carcinogenic effects of chromium are listed but not reviewed. Conclusions such as "no adverse health effects were reported," are not particularly helpful. The emphasis on chromium (VI) is appropriate, but this description might precede the pharmacokinetics section.

A more critical evaluation of the health advisory calculations would be desirable by, for example, reviewing possible sources of error, subpopulations to which the calculated health advisory may not apply, or information that is unavailable but would be critical for improving the calculation.

E. CYANIDE HEALTH ADVISORY

The health advisory for cyanide suffers from a haphazard literature review. For example, in the excretion section, three statements are presented. One is a summary statement about the major route of elimination, one refers to rats, and one describes an apparent human suicide attempt. A similar lack of critical interpretation appears in the section on longer-term exposure. Two dog studies are reported. In one, no signs of toxicity apparently were found after 3 mg/kg·day administration for thirty days. In the second, histopathological changes (in a site described as "ganglion cells of the CNS" with no other clarification) were found after 0.27 mg/kg·day for 15 months. In the first study, the cyanide was administered in the diet, in the second, as a capsule. Could the different findings be ascribed to the mode of administration? The text fails to discuss the differences.

The health advisory should add synonyms of prussic acid and hydrocyanic acid. The use of cyanides in electroplating and the need to check for cyanides in business closings are of concern but have been omitted. The section on occurrence should start with a definition of free cyanide. Many organic compounds exist, such as nitriles, which contain the cyanide functional group. Few nitriles disassociate to liberate the cyanide ion. Unless the definition of cyanides is limited to the cyanide ion and hydrocyanic acid, statements in the health advisory about pharmacokinetics should be modified.

Is it valid to apply potassium cyanide data to the case of hydrocyanic acid (or cyanide gas) when discussing percent absorption and time to death? The data of Getter and Baine would be better converted to cyanide ion as is done in the Criteria Document. Free cyanides absorb readily, and hydrocyanic acid is absorbed and distributed more rapidly than potassium cyanide. The distribution of cyanide depends upon the time before exposure and death; volatilization of hydocyanic acid from samples should be suspected when the analytical values are low. The wide range in the concentrations found in human organs in cases of fatal poisoning may be affected by these factors. The rapid distribution of cyanide throughout the organs of the body following ingestion or inhalation is an important fact in characterizing its effects. Yamamoto's data seem to indicate a greater tendency of cyanide to distribute to the liver and spleen by ingestion as sodium cyanide than by inhalation as cyanide gas.

The section on distribution needs to distinguish between the distribution of radioactivity and the distribution of cyanide. The accumulation of cyanide within erythrocytes is mainly due to the oxidation of iron in methemoglobin and the formation of cyanomethemoglobin. The section on metabolism should note that cyanocobalomin is a form of vitamin B-12. This nomenclature should be clarified for the non-expert reader. The effectiveness of different sulfur compounds that detoxify cyanide ion by forming thiocyanate is dependent upon the presence of a free sulfur atom adjacent to another sulfur atom in the the molecule as is the case with thiosulfate.

The discussion of human epidemiological studies in the section about health effects has omitted data on electroplaters.

The health advisory should note that animals can tolerate higher doses of cyanide when administered in the diet or in drinking water during longer-term exposures (20-90 days) than when the same dose is given over a much shorter period such as 1 day. The compound used in the study by Howard and Hanzal was hydrocyanic acid. The average concentrations were 76 mg/kg of diet and 190 mg/kg of diet, instead of 100 mg/kg and 300 mg/kg as described in the health advisory.

Why is Cyanide classified as a carcinogen? The health advisory reports that there is inadequate evidence for such a conclusion. Elsewhere, the health advisory states that there are no pertinent data available. This is contradictory.

The rate at which cyanide is absorbed, distributed and detoxified is important in evaluating the health effects of cyanides. For example, in the study by Palmer and Olson (see data below), it is not clear how much of the effect on liver is caused by greater total uptake of cyanide and how much by faster rate of absorption or distribution. This evaluation will affect the choice of data for calculation of the 1-day health advisory.

Compound	No-observed-effect-level	Duration of study
KCN diet	8 mg(CN-)/kg (body weight)·day	21 days
HCN diet	10.4 mg(CN-)/kg (body weight)·day	104 weeks
KCN water	12 mg/kg (body weight)·day	21 days

The Subcommittee could not find a rationale in the health advisory for the extra 5-fold factor in the safety factor. If this value relates to absorption characteristics, it would be better to describe it separately than to combine it with the traditional safety factor.

The Subcommittee has written a prose summary of the cyanide health advisory (See appendix) to illustrate the advantage of narrative for the reader lacking prior training in toxicology in comparison to the summary table of numerical data that the health advisory currently presents.

F. LEAD HEALTH ADVISORY

The recommended lifetime health advisory of 20 ug/day can be supported by present information about lead metabolism and toxicity. The calculations are correct, but the selection of values of a blood lead level of 15 ug/dl and a safety factor of 5 could be challenged. Although past evidence may have seemed inconclusive, the current literature supports an even lower level than 15 ug/dl, as discussed later in this review. The recommended standard represents a reduction in the interim EPA water standard for lead, currently 50 ug/liter. The Subcommittee also agrees that one day and ten day health advisories are not appropriate for lead. The health advisory generally is consistent with the Criteria Document. However, it does not have a clear focus and would not be especially useful to someone not thoroughly familiar with the lead literature.

An overall statement or description is needed on the range of health effects of lead, from the most mild to the most severe, associated with the corresponding blood levels. A summary statement about the significance of these findings should accompany the table.

In discussing absorption, the health advisory does not note the underlying reasons for enhanced absorption by children. This is a peculiar omission because of regulatory efforts to protect the young. The discussion of distribution is devoted solely to lead in blood and does not present information on where else lead may be found, for example, in kidney and bone. In the section on short-term exposure, several statements are made about the blood levels needed to achieve an effect and the possible latency to effects. These estimates are rather arbitrary and subject to change given current research findings. The statement that it takes 35 days for blood levels to reach a certain value is difficult to understand. The Criteria Document quotes evidence that it takes 100 days to attain a steady state level.

Because the health advisory does not describe complete dose-effect relationships, it is difficult to make sense of the biochemical, behavioral, neurophysiological and reproductive effects that are listed. The manner in which the health advisory chooses a single value of 15 ug/dl seems arbitrary. The change in blood pressure at approximately this level is similar in size to the elevation produced by barium, an elevation estimated to account for over 7,000 myocardial infarctions annually. In the health advisory for barium these data were not taken into account to lower the level.

The studies cited to illustrate the sensitivity of the fetus and child to lead need to be updated. The recent EPA-supported meeting in Edinburgh contained several reports indicating significant adverse effects in the offspring of mothers with blood lead values that previously would have been deemed low or modest. Some of these data, moreover, have been published. Research groups at the University of Cincinnati, Children's Hospital in Boston, and elsewhere have obtained data to indicate a direct relationship between maternal blood levels and lower birthweight, minor malformations, and reduced scores on psychological tests that persist for at least two years. Such data make the calculation of a threshold a tenuous proposition. Although impaired heme synthesis in children may occur at blood lead levels exceeding 10 ug/dl, the health significance of this effect is less clear.

For adults, as for children, earlier data suggested few significant effects on peripheral nerve function at blood leads below 40 ug/dl. Recent data support the occurence of such effects, but the case is not as clear, and the statement in the health advisory about nerve dysfunction should be made more provisional.

The proportionality constant between lead intake in the diet and blood lead needs to be reviewed in terms of diet contents such as other minerals. The statement about the World Health Organization European standard for lead of 100 ug/dl in blood should be re-examined to determine if it is cited correctly.

The Subcommittee questions the validity of the statement about the mutagenicity of lead. Because lead causes toxicity prior to mutagenicity does not mean no genotoxicity will result. In EPA's Air Quality Criteria Document, lead is described as decreasing the fidelity of replication, inhibiting RNA synthesis, causing an S-phase specific cell cycle block that indicates lead will interfere with normal synthesis and replication of DNA, and causing induction of DNA repair synthesis. Human carcinogenesis studies also can be cited in support of the genotoxicity of lead.

The lifetime health advisory for lead is less than levels sometimes found in air, food, and water. In the Criteria Document for lead, the lifetime health advisory is considered in terms of relative source data. This type of discussion might be included in the health advisory to reconcile the recommended level with actual intakes occurring for most Americans today.

For example, the following calculation for an adult ingestion level can be made using the relationship between blood lead levels and water lead levels derived by Pocock and coworkers.

$$\frac{(15\ \text{ug/dl})}{[(1\ \text{ug/dl})/(0.062\ \text{ug/day})](5)} = 48\ \text{ug/day}$$

where:

(a) 15 ug/dl = blood lead level at which no adverse effects are thought to be observed, and

(b) 5 = an uncertainty factor, which should have a rationale.

Using this maximum ingestion level dividing by an estimate of water consumption per day, a maximum level of lead in water is obtained. For example, if the estimate is two liters of water consumed per day by an adult, calculation is as follows:

$$\frac{48\ \text{ug/day}}{2\ \text{l/day}} = 24\text{ug/l}$$

Data on the relative sources of lead and how they contribute should be considered. The above calculations assume that 100% of an adult's lead exposure comes from drinking water. However, studies of other routes of lead exposure in adults show that air-borne lead, lead in food, and dust ingestion also

contribute. Drinking water contributes about 30% of total intake in adults of about 100 ug/day. Therefore, the calculation should be modified as follows:

$$\frac{(0.30)\ (48\ ug/day)}{2\ l/day} = 7.2\ ug/l$$

For this reason, a summary of the relative source contributions for adults and children will enhance the health advisory.

G. MERCURY HEALTH ADVISORY

The health advisory generally is consistent with the guidance in the Office of Drinking Water issue papers. The acceptable daily intake calculations are arithmetically correct. However, correcting the acceptable daily intake for intake of mercury from sources other than drinking water poses a difficult problem.

The decision to subtract mercury intakes for food and air from the total acceptable daily intake for inorganic mercury assumes that various forms of mercury are toxicologically equivalent.

The data in the health advisory support the conclusions in the context of a number of assumptions. The judgments reflect those in the Criteria Document. The major decision is to accept the experiment by Druet and coworkers as the basis of calculating the acceptable daily intake. The data of Fitzhugh and coworkers also are listed in the health advisory but not used. If they were used, the acceptable daily intake could be 240 times higher than that calculated in the health advisory. Human data on kidney effects from exposure to mercury vapor are not used. This is also true of the Criteria Document. Human data are variable in the case of mercury because humans react to mercury as an antigen, and the data may be difficult to evaluate for purposes of safety levels. However, human data are preferred, and there is a large data base for humans. The health advisory also neglects a rather sizable literature in children relating to Pink Disease (Acrodynia), which, despite its flaws, is still a better basis for quantification than the data from rats.

The assumptions and uncertainties are not clearly described, but it might require considerably more text to do this. The most important assumptions and decisions to be described are as follows:

- The rationale for choosing the data of Druet and coworkers versus those of Fitzhugh and coworkers.

- The assumption that all forms of mercury-mercury vapor in air, methylmercury in food and inorganic compounds in drinking water are toxicologically equivalent.

- The decision not to consider mercury intake from dental amalgams.

The approach to adjusting for other sources of mercury in the health advisory is to subtract the average total air and food intake of all forms of mercury from the total acceptable daily intake calculated for inorganic mercury. This calculation gives the acceptable daily intake for drinking water.

Another approach is to estimate the fraction of daily intake of total mercury contributed by each medium - air, food and drinking water - as estimated for the general "non-exposed" population and then to apportion the acceptable daily intake in the same proportion. For example, if drinking water accounts for 20% of total mercury, the acceptable daily intake for drinking water would be 20% of 11 ug/day of total mercury or approximately 2 ug/day, given a maximum concentration in drinking water of 1 ug/l, which is in agreement with the value derived by the World Health Organization.

A third approach is to consider the three major forms of mercury as toxicologically independent. Thus, the acceptable daily intake for inorganic mercury would be allocated almost entirely to drinking water, giving a maximum concentration in drinking water of 5 ug/l inorganic mercury.

Some data on mercury are missing from the health advisory that might better be included, such as:

- Information on intakes from food, air and water. These data should be described in the section on general information and properties.

- Intake from dental amalgams. This information also is missing from the Criteria Document.

- Concentrations of mercury found in commonly used indicator media, such as blood and urine, for the non-exposed general population. However, this information also is not present in the Criteria Document.

The health advisory is generally consistent with the Criteria Document. The problems of assessment reside mainly in the Criteria Document.

Mercury represents a special problem in its diverse toxic forms and how they differ in different media. In addition, this is the first attempt by any public health organization to evaluate the effects of ionic mercury in the context of total mercury intake. The Subcommittee has recommended that the Criteria Document for mercury undergo additional scientific and editorial review. Detailed comments on the Criteria Document by one Subcommittee member, which also suggest that the Criteria Document requires additional review, have been sent directly to the Office of Drinking Water.

H. NICKEL HEALTH ADVISORY

Some Subcommittee members have reservations about the proposed lifetime health advisory of 150 ug/l for nickel in drinking water (350 ug/l assuming that all nickel exposure occurs through drinking water) which is higher than the nickel concentrations that usually are encountered in public water supplies. However, EPA's Health Assessment Document for Nickel (Draft final; September, 1985) cites the results of the Agency's STORET data base as a range from <5 ug/l to >1,000 ug/l and gives values of 700 ug/l for the Ohio river. Other Subcommittee members think that setting the lifetime health advisory close to the usual drinking water concentrations is overly stringent and will result in frequent enforcement actions with no clear health benefits. These members recommend further EPA research on nickel carcinogenicity, sensitization and uptake in relation to chemical form (species).

The range of nickel concentrations in ambient surface water is not clear. In another study of 2503 water samples from 969 public water supplies in the United States during 1969-1970, nickel concentrations averaged 4.8 ug/l. The nickel concentrations were < 20 ug/l in 99.0% of the water supplies and < 50 ug/l in 99.9%. The highest observed nickel concentration was 75 ug/liter. Similarly, in running tap water from 20 public water supplies in Sweden and 10 European cities, the nickel concentrations ranged from 3 to 7 ug/l and 5 to 8 ug/l, respectively. In running tap water from 41 public water supplies in the environs of Copenhagen, Denmark, nickel concentrations were < 35 ug/l with two exceptions (91 and 120 ug/l). In Ontario, Canada, at the Sudbury site of the world's largest nickel deposits, mines and refineries, higher nickel concentrations have been reported in drinking water. Nickel concentrations in seven samples of running tap water collected in Sudbury during 1971-1972 averaged 200 ug/l (range = 141 to 264 ug/l), while corresponding values for five samples collected in Hartford, Connecticut, were 1.1 ug/l (range = 0.8 to 1.5 ug/l). Differences in ambient exposures to nickel were reflected by differences in the respective urinary excretions of nickel, which averaged 7.9 ug/day (5.9 ug/g creatinine) in 19 hospital workers who resided in Sudbury, compared to 2.5 ug/day (2.3 ug/g creatinine) in 20 hospital workers who resided in Hartford.

There is no current evidence to suggest that a carcinogenic response is induced in humans or laboratory animals by the ingestion of nickel compounds. However, the Criteria Document emphasizes that there are no bioassays for carcinogenesis of nickel by the oral route at concentrations greater than 5 mg/l. Until adequate oral carcinogenesis bioassays of nickel compounds in drinking water have been conducted, the question of nickel carcinogenicity remains open. This is one practical reason for selecting a lifetime health advisory level for nickel in drinking water close to the prevalent nickel concentrations in public water supplies in the U.S.

A second reason to set the health advisory level close to the levels observed in water is that hypersensitivity to nickel occurs in a significant portion of the general population, and clinical evidence suggests that oral ingestion can exacerbate nickel allergy. The Criteria Document summarizes the literature through 1982 on exacerbation of nickel contact allergy following oral intake and describes the occurrence of positive dermal patch test results from nickel in 7 to 11% of adult women and 0.2 to 2% of adult men. Because of the frequency of nickel hypersensitivity in the population, an additional margin of safety

may be appropriate in setting the health advisory level for nickel in drinking water.

A third reason to set the health advisory level closer to the levels observed in water is the growing evidence that bioavailability of nickel from drinking water may be greater than from foods and beverages. Solomons and coworkers have studied the effects of foods and beverages on gastrointestinal absorption of nickel in five healthy human subjects following an oral dose of 5 mg, administered as nickel sulfate hexahydrate. No significant post-prandial increases of plasma nickel concentration occurred after consumption of nickel added to beans or eggs, whereas prompt and sustained elevations of plasma nickel concentrations occurred when the same quantity of nickel was consumed as an aqueous solution by fasting subjects. Increases in plasma nickel concentration also were suppressed when 5 mg of nickel (as nickel sulfate) was dissolved in milk, coffee, tea, or orange juice. These studies indicate that certain foods and beverages reduce or prevent the absorption of divalent nickel from the alimentary tract. Foulkes and McMullen also have found that divalent nickel ion uptake from the lumen of the perfused rat jejunum is significantly inhibited by divalent zinc ion and by skimmed milk, supporting the view that certain dietary constituents reduce the bioavailability of nickel.

A fourth reason to set the health advisory level close to the levels observed in water arises from the methodological deficiencies of some published studies on reproductive effects of nickel salts, administered to rats in diet or drinking water. The limitations of these studies are discussed in the Criteria Document. A two-generation reproduction and fertility study of nickel chloride administered to rats in drinking water at three dosage levels is underway at the Research Triangle Institute under EPA sponsorship. The results of this study should soon be available. The outcome of this study is likely to influence the value of the lifetime health advisory for nickel in drinking water.

Oral carcinogenesis tests of nickel compounds added to drinking water might influence the level of the life-time advisory, as well as comparisons of the bioavailability and toxicity of nickel salts administered to rodents in drinking water. Until these data are available, EPA's criteria for regulating oral exposures to nickel in drinking water will remain controversial.

The health advisory does not contain an adequate discussion of nickel as an essential element. The statements in the health advisory about carcinogenicity are somewhat disconnected and mostly irrelevant. An interpretive summary would be far better.

I. NITRATE AND NITRITE HEALTH ADVISORY

The nitrate and nitrite health advisory is well-written and essentially complete. The health advisory fairly reflects the contents and conclusions of the Criteria Document. It is appropriate to recognize the infant as the most vulnerable organism.

The main thrust of the health advisory is that nitrate is not toxic per se, but must be converted to nitrite to be toxic. Nitrate reduction to nitrite is proposed to occur in saliva, which is then swallowed. Nitrate and nitrite are absorbed through the gastrointestinal tract. Nitrate is recycled by excretion into saliva, where conversion to nitrite occurs once again. Nitrite reacts predominantly with red cell hemoglobin to form methemoglobin and nitrate.

Nitrate and nitrite also produce profound vasodilation and cardiovascular collapse. The mechanism of vasodiliation is not clear. Formation of S-nitroso vasodilator compounds has been proposed as one mechanism, but is not mentioned in the Criteria Document. An alteration in chloride transport is another mechanism based on the competition of nitrate and nitrite with iodide and other monovalent cations.

The health advisory focuses on methemoglobin formation as the most significant health effect on the basis that infants suffer from methemoglobinemia after drinking nitrate contaminated water, milk or formula. For the purposes of the health advisory, methemoglobinemia in infants is the most appropriate endpoint. The calculated values assume a 10% conversion of nitrate to nitrite in the bucal cavity and 100% absorption of nitrite. The no-observed-adverse-effect--level selected from the studies reported in the Criteria Document is appropriate. The studies selected as the basis for the no-observed-adverse--effect-level are also appropriate. The calculations do not have arithmetic errors.

A major problem exists in the lack of data on the chronic health effects of nitrate. The lifetime multigeneration study of Newbern is controversial due to the intrepretation of the histopathology. The most recent cancer bioassay with Fisher 344 rats also is confusing due to the 100% tumor rate in both control and exposed animals.

No data are now available on the cardiovascular effects of chronic exposure to nitrate. Given the profound vasodilator effects of nitrates (some of which are used clinically) independent of the development of methemoglobinemia, this aspect of the toxicity of nitrate and nitrite deserves further investigation.

A more pressing problem is the question of the carcinogenicity of nitrate. The Subcommittee agrees with the health advisory conclusion that, under the Agency's proposed guidelines for carcinogen risk assessment, the current data fit best into category D (not classifiable). A major health concern, however, arises from the evidence that simultaneous ingestion of nitrite (or nitrate with amines) results in cancers of many organ systems. N-nitroso compounds are presumed to be the ultimate carcinogenic substances. The calculated excess cancer risk from the combined exposure to a nitrosatable compound and nitrite

can be significant. It is not possible to calculate the risk, if any, from nitrate or nitrite alone.

The Office of Drinking Water should devise a plan to develop appropriate experimental data to clarify this problem. Clearly a number of carcinogenic, nitrosatable compounds exist in drinking water or foods which, if ingested with nitrate or nitrite-contaminated drinking water, will result in formation of the carcinogens and excess cancer risk. Lacking better data, the Subcommittee agrees that a better estimate of human cancer risk can not now be provided, but the public is left uncertain if the present health advisory for nitrate provides adequate protection from this incremental risk.

Some of the difficulty arises from the legislative direction regulating drinking water standards. Like other health risk legislation, drinking water legislation is oriented to specific chemicals; e.g. nitrate rather than N-nitroso carcinogens. The Office of Drinking Water should consider and document how the current health advisory provides or does not provide a means of indirectly regulating human exposure to N-nitroso carcinogens.

The health advisory slips into jargon from time to time. The most glaring example is in the introduction, where the third paragraph refers to the "Health Advisory numbers". Clearly, this intended to mean the "Health Advisory values". This health advisory is better integrated than the other advisories for metals and related substances.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Metals Subcommittee
January 9-10, 1986

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COMMENTS SUBMITTED TO THE METALS SUBCOMMITTEE

BY THE PUBLIC REGARDING THE SCIENCE ADVISORY BOARD'S

REVIEW OF DRAFT DRINKING WATER HEALTH ADVISORIES

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Contact: Chuck Pace

Date: December 24, 1985

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Date: December 26, 1986

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Date: November 22, 1985

The New Jersey Dept. of Health
and The New Jersey Dept. of
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Contact: Bonnie L. Bishop

Date: August, 1985

State of Connecticut
Department of Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council

Contact: Martha Johnson

Date: December 12, 1985

POSTMEETING COMMENTS RECEIVED

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Contact: Chuck Pace

Date: January 27, 1986

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Metals Subcommittee

Open Meeting

Under Public Law 92-463, notice is hereby given that a two-day meeting of the Metals Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 9-10, 1986, in Conference Room 451 of the Joseph Henry Building; National Academy of Sciences; 2122 Pennsylvania Avenue, N.W.; Washington, DC. 20037. The meeting will start at 9:00 a.m. on January 9 and adjourn no later than 4:00 p.m. on January 10.

The purpose of the meeting will be to discuss draft drinking water Health Advisory documents for the following substances:

Arsenic	Lead
Barium	Mercury
Cadmium	Nickel
Chromium	Nitrate/Nitrite
Cyanide	

The Metals Subcommittee will not receive oral comments on the Health Advisory documents at the meeting. Written comments on any of the specific substances should be delivered within forty (40) days from the date of this notice to Manager, Health Advisory Program; Criteria and Standards Division [WH-550]; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460.

EPA's Office of Drinking Water prepared the draft Health Advisory documents. They are neither regulations nor regulatory support. To obtain copies of the draft Health Advisory documents for specific substances please write to the Manager of the Health Advisory Program at the above address.

The meeting will be open to the public. Any member of the public wishing to attend or to obtain further information should contact either Dr. Daniel Byrd, Executive Secretary to the Committee, or Mrs. Brenda Johnson, by telephone at (202)382-2552 or by mail to: Science Advisory Board (A-101F); 401 M Street, S.W.; Washington, DC: 20460, no later than c.o.b. on December 20, 1985.

Terry F. Yosie
Staff Director
Science Advisory Board

October 15, 1985

Date

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE
METALS SUBCOMMITTEE

Conference Room 451
Joseph Henry Building
National Academy of Sciences
2122 Pennsylvania Avenue, NW
Washington, DC 20037
January 9-10, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

Opening Remarks	.....	Dr. Weiss
Administrative Matters	.....	Dr. Byrd
Introduction	.....	Dr. Crisp Dr. Weiss

*Tentative Sequence of Reviews, beginning Thursday, January 9, 1986

Substance (Manager)		Reviewers
Arsenic (Marcus)		Drs. Wyzga and Gover
Lead (Marcus)	.....	Drs. Gover and Clarkson
Nickel (Rathija)		Drs. Sunderman and Brookmeyer
Barium (Bailey)	.....	Drs. Diamond and Sunderman
Cadmium (Bailey)		Drs. Mossman and Diamond
Chromium (Bailey)	.....	Drs. Brookmeyer and Mossman

On Friday, January 10, 1986

Mercury (Khanna)		Drs. Clarkson and Wyzga
Cyanide (Rathija)	.....	Drs. Ferrand and Kuschner
Nitrate (Bailey)		Drs. Menzel and Ferrand

At the conclusion of the reviews

*Completion of reviews (previously deferred)	Dr. Weiss
General comments	Dr. Weiss
Nomination of Criteria Documents for further review	Dr. Weiss

Other Subcommittee Business

Concluding remarks	.....	Dr. Weiss Dr. Byrd

ADJOURNMENT

* The sequence in which the Subcommittee reviews Health Advisories for different substances and the time allocated to each review are at the discretion of the Chair.

CYANIDE

DEFINITION

For the purposes of this document cyanide refers to hydrogen cyanide and its water soluble salts, primarily sodium and potassium. Organic compounds called nitriles because they contain a cyano, (-CN), functional group are sometimes referred to as cyanides. These are not included because they do not readily dissociate to form cyanide ion. Cyanide ion has a tendency to combine with certain cations to form complexes. Their contribution to the "free" cyanide measured in water solution depends on their stability and the analytical procedure.

Pure hydrogen cyanide is a colorless liquid with a bitter almond taste which biols near room temperature (25.7^{o} C) and is miscible in all proportions with water. Sodium and potassium salts are colorless, crystalline solids which are quite soluble in water where they are converted to hydrogen cyanide to an extent dependent upon the acidity of the water.

SOURCES OF CYANIDES

Cyanides are used by the chemical industry in the manufacture of pesticides, rodenticides, photographic and metal polishing products and in the preparation of other chemicals such as nitriles and plastics. Wastes from the manufacture or use of cyanide products, for example, from electroplating and case hardening operations are potential sources of cyanide contamination of water supplies.

Cyanide, at the concentrations normally found in drinking water supplies, ordinarily is not an important contributor to the body intake. Therefore, it is not a public health problem in the United States. A survey reported in 1970 of 2595 samples collected from over 800 water supplies found a maximum concentration of 0.008 mg per liter. Nevertheless, the possibility of cyanide in water supplies by accidental or intentional contamination requires that monitoring programs or at least an anlytical capability should be maintained by water suppliers.

There are other contributors to the body burden which should be considered if cyanide is a concern. Unusual diets, smoking habits and occupational exposures can be more important contributors than drinking water. Individuals with a metabolic defect in the enzyme system that converts cyanide to less toxic thiocyanate, with a vitamin B12 deficiency or with defective B12 metabolism or with an iodine deficiency, as well as fetuses in utero of smoking mothers, are at greater risk than the normal population.

There is no available evidence pertaining to the carcinogenicity of cyanides.

ADVERSE HEALTH EFFECTS

Cyanide acts as an asphyxiant by preventing body tissues from using the oxygen transported to them by the blood. Thus, the inhalation, ingestion or absorption through the skin of high concentrations of cyanide can cause serious damage to the tissues of many organs. Hydrogen cyanide is absorbed most rapidly by inhalation.

Studies relating cyanide exposures to adverse health effects indicate that a daily intake of up to 0.021 mg of cyanide per kg of body weight over an extended period will not cause observable adverse effects to the health of children. If all exposure comes from drinking water, then to avoid exceeding the daily dose, the concentration of cyanide in the water supply must not exceed 0.21 mg per liter of water. This value is based upon the assumption of a 10 kg child who drinks an average of 1 liter per day:

$$\frac{0.21 \ \frac{\text{mg } CN^-}{\text{kg (bw) day}} \times 10 \text{ kg (bw)}}{1 \ \frac{\text{liter}}{\text{day}}} = 0.21 \ \frac{\text{mg CN}}{\text{liter}}$$

A 70 kg adult drinking 2 liters per day from this same water supply will receive a considerably smaller daily exposure per kg of body weight.

$$\frac{0.21 \ \frac{\text{mg } CN^-}{\text{liter}} \times 2 \ \frac{\text{liter}}{\text{day}}}{70 \text{ kg (bw)}} = 0.006 \ \frac{\text{mg } CN^-}{\text{kg (bw) day}}$$

REMOVAL OF CYANIDE FROM WATER SUPPLIES

Cyanide ion, CN^-, in water is in equilibrium with hydrocyanic acid (HCN) with the equilibrium concentrations dependent upon the pH of the water:

$$CN^- + H_2O = \begin{matrix} HCN\ (gas) \\ | \\ HCN\ (aq) \end{matrix} + OH^-$$

At pHs less than 7, over 99% will be in the HCN (aqueous) form. Therefore, in an open body of water there will be a tendency to lose cyanide slowly by evaporation as gaseous HCN. Chlorination of the water supply or use of other oxidizing substances for disinfection will convert some cyanide to the less toxic isocyanate form.

ANALYSIS OF WATER FOR CYANIDES

Free CN^- can be measured: by titration with silver ion using a silver sensitive indicator; by colorimetry based upon conversion to cyanide chloride using chloramine followed by formation of a dye, or by cyanide-selective electrode.

Depending on the pretreatment method used in the analysis, anything from free cyanide to total cyanide, including insoluble and complex cyanides, can be determined.

REFERENCES

United States
Environmental Protection
Agency

Office of the Administrator
Science Advisory Board (A-101)
401 M Street, SW
Washington, DB 20460

SAB-EHC-87-005
October 1986

Review of Drinking Water Health Advisories by the Halogenated Organic Subcommittee of The Environmental Health Committee of The Science Advisory Board

- Carbon tetrachloride
- Chlorobenzene
- Dichlorobenzenes (ortho, meta and para)
- 1,2-Dichloroethane
- cis-Dichloroethylene
- trans-Dichloroethylene
- Vinylidene chloride
- Dichloromethane
- Dichloropropane
- 2,3,7,8-Tetrachlorodibenzo-p-dioxin
- Epichlorohydrin
- Hexachlorobenzene
- Polychlorinated biphenyls
- Tetrachloroethylene (perchloroethylene)
- 1,1,1-Trichloroethane (methylchloroform)
- 1,1,2-Trichloroethylene
- Vinyl chloride

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SAB-EHC-87-005

September 20, 1986

OFFICE OF THE ADMINISTRATOR

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board [A-101]
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Dr. Griesemer:

On January 14-17, 1986 the Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee reviewed fifteen (15) draft health advisories for drinking water in public session. The draft health advisories were prepared by the Office of Drinking Water. The health advisories are not regulatory documents but are intended to provide consistent, brief reference information, particularly for technical personnel responsible for the operation of water works or for state and local public health officials. During the review, the Subcommittee utilized Drinking Water Criteria Documents as support information for all of the health advisories except for 1,2-dichloroethane, for which the Subcommittee made use of the Agency's Health Assessment Document, supplemented by a Quantitative Toxicological Evaluation for drinking water. Some of the Criteria Documents merit detailed review in the future.

Our comments below are generally divided into general advice, which is relevant to all of the advisories reviewed by the Halogenated Organics Subcommittee, followed by scientific advice specific to each of the substances reviewed. Because of the extensive nature of the comments, a Table of Contents and some supporting appendices are included. We appreciate the opportunity to become involved with this program and stand ready to provide further advice, as requested.

Sincerely,

John Doull, M.D., Ph.D.
Chair, Halogenated Organics Subcommittee

Seymour Abrahamson, Ph.D.
Vice-chair, Halogenated Organics Subcommittee

EPA NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency, and hence the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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I. GENERAL COMMENTS OF THE HALOGENATED ORGANICS SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA'S SCIENCE ADVISORY BOARD REGARDING DRINKING WATER HEALTH ADVISORIES

The Subcommittee recommends that each halogenated organic health advisory provide the CAS number after the chemical name on the first page to facilitate referencing, and that each health advisory provide access information (such as a name and telephone number) for the chemical manager or health advisory manager.

The Subcommittee suggests that the health advisories cite a date through which the literature has been searched comprehensively, and give preference to the use of primary literature citations, whenever they are available. If relatively inaccessible references, such as EPA documents or in-house memoranda, must be used, the health advisory should explain how to obtain them. Citation of abstracts or personal communications should generally be avoided. English translations of any critical foreign language documents used in the health advisory should be made available upon request. Whenever primary reference documents, such as Criteria Documents or International Agency for Research on Cancer publications, are cited, EPA should provide specific page numbers in the reference section. Otherwise, the health advisory as a quick reference will lose value, because a large number of volumes would have to be searched.

The Subcommittee recommends that the Office of Drinking Water provide a consistent and uniform list of physical and chemical properties for each substance. These properties should be presented in a uniform system of units, and should contain factors for converting concentrations between different media. If the literature does not include one or more properties, the health advisory should indicate this absence, rather than omit the property from the list. The Office of Drinking Water should add a glossary of definitions, abbreviations, and acronyms. Situations will occur in which the analytical measurement of the concentration of a substance in water exceeds its solubility when, for example, the water sample contains undissolved substance or when other contaminants enhance solubility. However, it will be worthwhile to compare the levels recommended in each health advisory to the solubility of a substance in pure water since, in some cases, the former exceed the latter.

The description of the occurrence and use of a chemical should include a single primary reference. Whenever available, sections on use and human exposure should be included in the Criteria Documents and health advisories. Occurrence information should be put into perspective with health effects information in the health advisories. Uses listed in the health advisories should be categorized as "past" versus "current," when applicable, but both should be included.

Pharmacokinetic sections should include the half-life of the chemical in humans and/or animals, and the rates of absorption and excretion, where known. This information will be helpful in assessing blood levels which correspond to toxic endpoints. It will also enable the reader to be aware of the persistence of the chemical in the biological system being discussed. Most of the Criteria Documents for halogenated organic chemicals contain this information for some route of administration.

A default assumption of a 20% source contribution of drinking water to total human exposure should not be made: (1) if available exposure estimates indicate that air and/or food are not a major source of exposure, or (2) if the physico-chemical properties of a compound make one or both alternative sources of exposure (food or air) unlikely.

The rationale for the 20% assumption is an estimate of the generic contribution of water to total dose. The assumption of 100% source contribution is appropriate for substances for which exposure occurs mostly through drinking water ingestion, as in the two circumstances above.

The health advisories should indicate that calculations are based on the assumption that the only increase in exposure occurs through drinking water. There may be additional exposure by other routes such as inhalation of vapors from the boiling of water, through showering and by dermal absorption when bathing. Boiling water, except outdoors, should not be recommended for decontamination purposes, since boiling water will transport a halogenated organic material from drinking water into indoor air, where it recirculates, changing the route of administration to inhalation and possibly increasing exposure. Non-water sources of exposure may include food and air. Health advisory recommendations should take into consideration these additional sources of exposure.

The sections about health effects should be reorganized. Human health effects should be presented first, followed by discussion of health effects in animals. Each health advisory should categorize the effects derived from human and animal data in parallel structures. An example is presented below:

(1) Human evidence:

(a) Acute (brief) exposure or toxicity
(b) Repeated short-term exposure or toxicity
(c) Chronic (long-term) exposure or toxicity
(d) Specific organ system effects and/or mechanism
(e) Carcinogenicity and mutagenicity
(f) Reproductive and developmental effects

(2) Animal and other evidence:

(a) Acute (brief) exposure or toxicity
(b) Repeated short-term exposure or toxicity
(c) Chronic (long-term) exposure or toxicity
(d) Specific organ system effects and/or mechanism
(e) Carcinogenicity and mutagenicity
(f) Reproductive and developmental effects

Each of the above categories should include the exposure levels known to cause and not to cause effects. The human evidence category should include experience from the medical, poison control, occupational, and epidemiological literature. In particular, the health advisory should emphasize studies of

groups exposed to contaminated water. Mutagenesis data should be preceded by a statement indicating that positive results may indicate the potential of the chemical to initiate genetic changes that may lead to cancer but may not indicate developmental or reproductive risks.

The Subcommittee recommends that when a health advisory uses data from a particular study for a calculation of the no-observed-adverse-effect-level or lowest-observed-adverse-effect-level, this use should be highlighted as the study is discussed. Otherwise, the user has to flip back and forth in a health advisory and can not easily refer to the data on which the health advisory was based.

Determining a lowest-observed-adverse-effect-level or no-observed-adverse-effect-level from an oral exposure study, especially oral exposure through drinking water, is preferred to a determination using data from other routes of exposure. For some chemicals, oral exposure data may not be available, making it necessary to rely on data derived from other routes of exposure, such as inhalation. When data from an inhalation study are used, factors such as the body weight, tidal volume and respiratory rate of the animal should be considered in the calculation of the total absorbed dose. An uncertainty factor can then be applied to the animal estimate to calculate the health advisory level. Inhalation data also can be used to increase confidence in the calculations derived from drinking water studies. It might be remembered, however, that pharmacokinetic factors, such as differences in absorption rate and first pass effects, may produce predictable differences among different routes of exposure, which in the absence of data on comparable blood levels must be interpreted with caution. Development of a data base comparing the toxicity of halogenated organic chemicals at similar blood levels from studies using different routes of exposure would be desirable; comparisons could be made between various hydrocarbons and between different routes of exposure. Where the appropriate data are not available, EPA should consider these issues as research needs.

In assigning a lowest-observed-adverse-effect-level or a no-observed-adverse-effect-level, EPA should consistently use a dose-related endpoint for a particular effect. Thus, the use of one toxicological endpoint in one health advisory should be consistent within the same advisory as well as between advisories. If a decrease in body weight is used as an endpoint, significant weight loss should not be ignored in other advisories. Similar arguments apply to other endpoints, such as serum enzyme levels, histopathological changes and organ weight changes.

The Subcommittee recommends that the definition of the term "longer-term advisory" include the length of time covered, i.e. month to years. An advisory that recommends a lower level of a substance for a 10-day health advisory than for a longer term (or life-time) exposure level contradicts a principle of toxicology. From the managerial view, once people are exposed to a low level of a substance in drinking water, a higher long-term health advisory value implies that exposed persons will be safer, if they would continue drinking the contaminated water. For most substances, a greater effect is manifest as the duration of an exposure increases. Either interpretation, acute or chronic, could be in error. For certain substances, especially those causing neurotoxic effects, a phenomenon of tolerance can occur. However,

tolerance usually is induced by increasing the dose over time. Even with a substance causing tolerance, safety levels should not be based on the chronically exposed animal, if exposure to this level would cause toxic effects in the previously unexposed person. The problem of health advisory values that are inconsistent with time of exposure may arise when different routes of exposure, different species or different endpoints of toxicity are used for the development of the various health advisories for a substance. In these situations, EPA should explicitly state when the inconsistency arises from the choice of safety (or "uncertainty") factors. The Subcommittee suggests that in these instances the levels derived for longer-term or lifetime health advisories should be used to calculate 10-day and 1-day health advisories.

The Subcommittee believes that the mathematical calculations of health advisory levels are informative, where directly relevant. However, for substances where argument is developed by analogy to another compound, discussion should focus on the strength or weakness of the analogy. Illustrative calculations in these circumstances do not communicate the uncertainty involved in the analogy, and they imply the possession of information that does not actually exist. The health advisory should present alternative analogies and emphasize their comparative strengths and weaknesses.

Statements regarding potential carcinogenic risks should clearly state that the values given represent an estimated plausible upper bound on the possible true risk. For example, a health advisory introduction should state that, for given concentrations of the contaminant, the actual risks are unlikely to exceed the projected excess lifetime cancer risks calculated by EPA. In the section about evaluations of carcinogenic potential, the health advisories should note that the exposure levels provided are unlikely to pose a carcinogenic risk in excess of the stated values. Under "Other criteria, guidance, ..." risks of 10^{-5}, should be changed to "estimated upper limits of 10^{-5}, ...". The intended readers of the health advisories, including operating personnel of water works, probably do not have the technical background to supply the appropriate perspective themselves, which may prove crucial in some decisions.

The Subcommittee requests that the Drinking Water Subcommittee and/or the Environmental Health Committee comment on the revisions of the classification levels of cancer in the Federal Register on pages 46884-46885 as 40 CFR Part 141.142. EPA has moved all group B probable human carcinogens (both group B1 and B2) into a new category 1 of known or probable human carcinogens, which receive equal treatment. Both the International Agency for Research on Cancer categories and EPA's guidelines for carcinogen risk assessment distinguish probable human carcinogens from known human carcinogens. Strict use of the new classification approach might treat a substance as an aqueous carcinogen based on an evaluation of positive inhalation data, with contradictory data for drinking water. Such might be the case with arsenic, for which the Agency has evaluated the literature differently for drinking water.

Health advisories include standards derived by other groups, such as the Occupational Safety and Health Administration, National Institute of Occupational Safety and Health, American Conference of Government Industrial Hygiensts, World Health Organization and National Academy of Sciences.

References to these standards will be of greater value to readers if each health advisory supplies the assumptions made and/or constants used in the derivation of quoted standards. A statement could be made for each standard concerning the endpoints(s) on which the standard was based, the estimated risk and the date the standard was issued. Conversion of such standards to dimensions equivalent to those of drinking water exposures would facilitate comparison. However, some members of the Environmental Health Committee caution that such comparisons can mislead the reader if not properly explained. The Subcommittee also recommends that the health advisories cite Science Advisory Board reviews and the EPA reports where the substance in question was previously reviewed. Otherwise, state and local public health officials will not be aware of the context in which the Board's comments are made.

EPA needs a source document for polychlorinated biphenyls. The Subcommittee has provided a detailed scientific review of the Drinking Water Criteria Document for Polychlorinated biphenyls to the Office of Drinking Water, which included thirty detailed comments and thirteen minor comments. The final draft of this document is dated March, 1985. The data and papers which are included, and some of the interpretations, are highly inadequate. Some of the issues, which have not been thoroughly discussed or even acknowledged, include the following:

- Recent papers indicate that Yusho poisoning is primarily related to the toxic polychlorinated dibenzofurans and not the polychlorinated dioxins in contaminated rice oil. Thus, a discussion of the human health effects of polychlorinated biphenyls should not use "Yusho" as an example. Industrial exposure data more accurately reflect human health effects.

- The discussion of chemical analysis of polychlorinated biphenyls and the complexity of polychlorinated biphenyl mixtures is out of date, and any revised document should recognize important new advances in this field.

- A multitude of important papers on structure-activity relationships for polychlorinated biphenyls have been published but are not cited in the comment. For polychlorinated biphenyls, this is a critical issue which must be thoroughly discussed.

- The mechanism of action of polychlorinated biphenyls has been extensively reviewed but is not covered adequately in the Criteria Document. [See, for example, CRC Crit Rev. Tox 13: 319 (1985), Environ. Health. Perspect. 60: 47 (1985) or Environ. Health. Perspect. 61: 21 (1985)]. These sections of the Criteria Document are out of date and need revision.

In view of the above comments, as well as those made beginning on page 26, the Subcommittee strongly recommends that the Drinking Water Criteria Document for Polychlorinated biphenyls be extensively revised and updated. The revised document could serve as an Agency-wide source document.

II. SPECIFIC COMMENTS OF THE HALOGENATED ORGANICS SUBCOMMITTEE ON SEVENTEEN DRAFT DRINKING WATER HEALTH ADVISORIES

A. CARBON TETRACHLORIDE HEALTH ADVISORY

The health advisory for carbon tetrachloride is not a legally enforceable federal standard. However, any EPA guideline that quantifies risks will be used as policy by Federal, state and local officials, as well as the public, including the affected industries. In a very practical way, they also become the reference points in litigation proceedings. It is, therefore, desirable that the EPA initially examine a complete data base in preparing the carbon tetrachloride health advisory, although the health advisory does not need to cite the complete literature. The criterion applied is whether the health advisory cites the literature that is crucial to the calculations. Evaluation, interpretation and ultimate utilization of data must be done in an objective way, if the health advisory is to have credibility. The Criteria Document should provide much of the evidence for such a process. However, critical data are excluded in the case of the carbon tetrachloride health advisory.

The support document for the health advisory is the final draft Criteria Document prepared by Life Systems, Inc., which is dated January, 1985. This document represents a condensed version of the more comprehensive, and supposedly multimedia, Health Assessment Document, which was published by EPA in September of 1984. As the Subcommittee understands it, the Health Assessment Document contains data from the health effects literature up to March 1983, and was based in part on the Criteria Document, which appeared in draft. One would assume that the Criteria Document would be more up-to-date, but it contains about one-half as many references as does the Health Assessment Document. It should be pointed out that since March 1983, there have been over one thousand citations in the toxicologic literature related to carbon tetrachloride. Several of these new articles are pertinent to the health advisory and should be incorporated. Where appropriate, references to recent key studies are provided in these comments.

EPA recently issued a final rule for a Recommended Maximum Contaminant Level for carbon tetrachloride at the level of zero based on a B2 carcinogenicity classification with evidence from three animal species by the oral route. The same rulemaking reports that carbon tetrachloride has been detected in drinking water supplies in concentrations ranging from 0.5 to 30 parts per billion (ppb). The Agency's cancer risk estimate (parts per billion) corresponding to an upper bound of 10^{-5} risk) given in the rulemaking is 0 - 2.7 cases. The Office of Drinking Water should note the upper bound nature of the risk estimate. EPA also proposed a Maximum Contaminant Level for carbon tetrachloride (Federal Register, pp. 46902-46933, November 14, 1985) at 0.005 ppm. This rulemaking also proposes 5 ppb as the practical quantitative level of detection of carbon tetrachloride in water. The above numerical estimates of carbon tetrachloride risk or numerical contaminant levels need to be acknowledged, accounted for, and explained in the drinking water health advisory, if the advisory is to be useful for state and local public health officials.

The above comments serve to indicate that the Criteria Document is incomplete. The resulting drinking water health advisory, therefore, is not based on all of the readily available data and merits revision. The Subcommittee recommends either a further scientific review of the Criteria Document, or (better) an updating of the Health Assessment Document, perhaps by a memorandum (or "quantitative toxicological evaluation") and use of the combined Health Assessment Document and memorandum as the reference (or source) document to support the drinking water health advisory.

In the section on "general information and properties," the synonyms section should omit "carbon tetrachloride," and add "methane tetrachloride" and "perchloromethane". Under "properties," the odor threshold may not be known, but the odor is sweetish, aromatic, and moderately strong. The odor of carbon tetrachloride is characteristic. Under "occurrence," after the first two paragraphs the remainder of this section runs together and should be revised to state how carbon tetrachloride gets to air, to water, etc. How much is found in an environmental sink, how long does it stay, and what are the major concerns? There are no references provided in this section of the drinking water health advisory. The Criteria Document has no section on occurence. This section needs a few key citations to support the statements, judgements, assumptions and uncertainties in this section.

The pharmacokinetics section illustrates the desirability of providing succinct, meaningful summaries. The paragraph provided could be replaced with one which states that, based mostly on animal studies, carbon tetrachloride has been shown to absorb readily through the respiratory tract, the gastrointestinal tract, and the skin. The subsections about distribution, metabolism, and excretion should be revised to provide the basis of the information cited, if the health advisory is to be useful for health professionals.

In the health effects section, the following additional references, which are not covered in the drinking water health advisory and/or Criteria Document for chloroform, should be reviewed and utilized in the overall toxicological evaluation:

(a) Amacher, D.E. and Zelljadt, I., "The morphological transformation of Syrian hamster embryo cells by chemicals reportedly nonmutagenic to Salmonella typhimurium," Carcinogenesis (Lond.) 4: 291-296 (1983).

(b) Gans, J.H. and Korson, R., "Liver nuclear DNA synthesis in mice following carbon tetrachloride administration or partial hepatectomy," Proc. Soc. Exp. Bio. Med. 175: 237-42 (1984).

(c) Mirsalis, J.C.; Tysn, C.K.; Loh, E.N.; Spek, D.K. and Spalding, J.W., "Induction of hepatic cell proliferation and unscheduled DNA synthesis in mouse hepatocytes following in vivo treatment," Carcinogenesis 6: 1521-4 (1985).

Shank, C. and Barrows, L.R., "Toxicological effects on carcinogenesis," in Toxicological Risk Assessment, Vol. I of Biological and Statistical Criteria, D.B. Clayson, D. Krewski, and I. Munro, eds., CRC Press, (1985), p. 93.

Sina, J.F.; Bean, C.L.; Dysart, G.R.; Taylor, V.I. and Bradley, M.O., "Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential," Mutat. Res. 113: 357-91 (1983).

Uemitsu, N.; Minobe, Y. and Nakayosho, H., "Concentration-time-response relationship under conditions of single inhalation of carbon tetrachloride," Toxicology and Applied Pharmacology 77: 260-266 (1985).

VanStee, E.W.; Boorman, G.A.; Moorman, M.P. and Sloane, R.A., "Time-varying concentration profile as a determinant of the inhalation toxicity of carbon tetrachloride," J. Tox. Enviro. Health 10: 785-795 (1982).

Wilkcosky, C.; Checkoway, H.; Marchall, E.G. and Tyroler, H.A., "Cancer mortality and solvent exposures in the rubber industry," Am. Ind. Hyg. Assoc. J. 45: 809-811 (1984).

The human exposure section of the Criteria Document was unavailable for review and comment.

The entire section on "quantification of toxicological effects" rests upon data derived from an EPA sponsored study performed by J.V. Bruckner and co-workers. The paper was recently published in Fundamental and Applied Toxicology 6: 16-34 (1986). It was only accepted for publication in May 1985, but EPA has used it in risk assessments for carbon tetrachloride for more than a year. A copy of this paper was obtained and reviewed by one member of the Subcommittee. This paper presents primarily clinical chemistry data for rats that were dosed for nine days or twelve weeks. Many methodology problems were immediately evident. Only male rats were used. Dosing was discontinuous (i.e., for 9 days: 5 on, 2 off, 4 on); for 12 weeks: 5 on, 2 off, for duration). Animals were not fasted; dosing was conducted at night (initial part of active cycle) because the authors determined that this period is when non-fasted rats are most sensitive to carbon tetrachloride hepatotoxicity. No signs of toxicity or body weight data were provided. Carbon tetrachloride was administered by gavage in corn oil. The Science Advisory Board previously has noted the controversy about the significance for environmental standards of data obtained using corn oil as vehicle. No chemical analyses were provided for carbon tetrachloride, corn oil, or feed. The results were based exclusively on liver enzyme and pathology data.

In the section about quantification of toxicological effects, the data of Bruckner may be appropriate for calculating the 1 and 10 day drinking water health advisories, but they should not be used for the longer term health advisory. There are papers, cited in the Health

Assessment Document, by Smyth and coworkers (1936), Adams and coworkers (1952) and Prendergast and coworkers (1967), which are as suitable as the Brucker data for the calculations, since there is some validity in extrapolating from inhalation to oral exposure. (See K. Khanna, "Use of Inhalation Data for Estimating Acceptable Exposure Levels in Drinking Water," draft, September 12, 1985, EPA issue paper).

The section on quantification of toxicological effects presents health advisories for one day (based on a ten kg child), ten days (based on a ten kg-child), and longer term (for both a ten kg child and a seventy kg adult). Health advisories for one-day and ten-days for a 70 kg adult are missing. The Criteria Document includes these calculations, and they should be included in the health advisory.

There is inconsistent use of data in calculating the RRfd, DWEL, and unit risk estimate for carcinogenic potential. The first two are based on Bruckner's data. The latter values derive from four studies which by EPA's own admission, are "less than ideal for risk estimation for continuous daily exposure over a lifetime." EPA has chosen to estimate unit risk by the geometric mean of the estimates from each of the studies (two in mice, one in the rat and one in the hamster). This is a poor estimate because the geometric mean of four poor estimates is still a poor estimate. EPA should make an effort to provide a more accurate evaluation of carcinogenic potential, or it should describe the uncertainty in the estimate in more detail.

The lifetime health advisory, whether revised or not, should be placed into perspective with the levels of carbon tetrachloride expected in water and other environmental media.

In the section about other criteria, guidance and standards, paragraphs 1, 2, 3 and 4, should be combined or discussed in the section on evaluation of carcinogenic potential (section V).

Since apparently suitable data now are available (i.e., those of Bruckner), what do the calculations in paragraph 5 of section V mean? A better explanation needs to be provided.

Since SNARLS have been replaced by RRfd's, why include them? Overloading the drinking water health advisory with numbers is not helpful.

B. CHLOROBENZENE HEALTH ADVISORY

The spectrum of chlorobenzene induced acute and chronic toxic effects is well-documented in animal experiments for different routes of exposure. Limited human data indicate similarities between man and various animal models. There is also some evidence that chlorobenzene causes neoplastic nodules in male rats, leading to its classification as a Group C carcinogen under EPA's proposed carcinogen risk assessment guidelines. The Science Advisory Board reviewed the Criteria Document for Monochlorobenzene in public session on July 23-24, and a detailed written report is in progress.

In the section about quantification of toxicological effects, the advisory notes that numerous correlations exist between the toxicities, such as liver necrosis and porphyria, versus subcellular events, such as enzyme induction, covalent binding and glutathione depletion. However, in the light of conflicting results, the mechanistic meaning of these correlations ought to be viewed with caution.

An appropriate 10-day (and 1-day) health advisory for chlorobenzene was developed based on an inhalation study. This is compatible with a regulatory philosophy of public health prudence, since after inhalation exposure less of the material goes directly to the liver to undergo metabolism. Thus, there is less of a "first pass" effect, and the inhalation data are likely to represent a more toxic route of exposure than oral administration. The selection of the Battelle studies for both the long term health advisory and the life time health advisory appears sound, as does the quantification of carcinogenic effects.

The criteria document is inconsistent with the health advisory in places, and the health advisory makes inconsistent statements regarding the mouse studies.

The Subcommittee questions why data were not used from the 14-day toxicity study sponsored by the National Toxicology Program. If these values are used, and if animal factors (not human factors) are applied to the animal data, then the shorter term health advisories become consistent with the longer term. Further, if the National Toxicology Program data are used, problems with the absorption fraction are resolved. The Subcommittee notes that the National Toxicology Program usually performs histopathology analyses as part of its 14-day studies.

The Office of Drinking Water should clarify why 125 mg was chosen as a no-observed-effect-level, when growth retardation occurred with the male mouse at 60 mg.

Some perspective will be useful in statements about biodegradation, perhaps by comparing chlorobenzene to other substances, such as hexachlorobenzene, which biodegrades about 1,000 times more slowly. A direct statement of the half-life of chlorobenzene would be useful.

C. DICHLOROBENZENES (ORTHO-DICHLOROBENZENE, META-DICHLOROBENZENE AND PARA-DICHLOROBENZENE) HEALTH ADVISORIES

The health effects section notes that a reasonably well developed data base exists for the toxicity of dichlorobenzenes from animal experiments. Data from various groups of investigators suggest that the spectrum of toxic effects is similar with the three isomers in various species. Limited human data also suggest similarities between man and animals in the manifestations from acute or chronic exposure to dichlorobenzenes. State-of-the-art developmental and reproductive toxicity studies did not reveal any adverse effects. National Toxicology Program carcinogenicity studies in two rodent species indicated a lack of tumorigenic effects of o-dichlorobenzene. Dichlorobenzenes are not mutagenic in animal studies and in some other commonly used mutagenicity assays, but they show some mutagenic effects in onion, fungal and yeast systems.

The pharmacokinetics and disposition of the three isomers also are quite similar with the exception that substantial amounts of mercapturic acids are formed from o-dichlorobenzene and m-dichlorobenzene but not from the para-isomer. Both o- and p-dichlorobenzene cause similar toxicities at comparable dosage levels. O-dichlorobenzene depletes glutathione levels, whereas p-dichlorobenzene does not affect glutathione levels. Thus, it is unlikely that glutathione depletion represents a major mechanism of dichlorobenzene toxicity. To the contrary, the data indicate that the mechanism of toxicity of dichlorobenzenes has little, if anything, to do with glutathione depletion or related oxidative stress. Similar problems exist with attributing any role in dichlorobenzene-induced toxicity to reactive intermediates. Considering the high doses required to induce subchronic and chronic toxicity, it is more reasonable to assume that nonspecific membrane effects or interference with hormonal homeostasis is involved in the induction of toxicity, as has been shown for some other chlorinated benzenes. Since specific evidence for dichlorobenzenes is lacking for the latter contention, it must be concluded that the mechanism of action of these compounds is unknown.

In the section about quantification of toxicological effects, development of drinking water health advisories for dichlorobenzenes has been conducted according to EPA's issue paper. Selection of the Battelle studies for the recommended 1-day and 10-day health advisory levels and for acceptable daily intake calculations is reasonable because these bioassays are scientifically adequate. Studies of Varshavskaya indicating orders of magnitude lower no-observed-effect--levels for dichlorobenzenes contrast with a larger number of investigations which yield consistent but different results. Because the details of this study are very sketchy, this study should not be used for health advisories. It is also prudent to use oral gavage data rather than inhalation data to derive recommendations for health advisories because chemicals that are readily metabolized may have vastly different toxicities when administered by these

two routes. Furthermore, in the Battelle studies, dichlorobenzenes were administered in corn oil which leads to essentially complete absorption. However, chlorinated benzenes administered in aqueous solutions are absorbed to a much lesser extent. This introduces a further conservative element into the estimation of the no-observed-effect-level.

The solubility noted in the health advisory is in error.

The health advisory should use an absorption fraction of 60% to be consistent with the available information on absorption.

The term "relatively high absorption" could be better stated in quantitative terms.

D. 1,2-DICHLOROETHANE HEALTH ADVISORY

The Science Advisory Board previously reviewed the health effects data for 1,2-dichloroethane in a report of January 4, 1985, which the Halogentated Organics Subcommittee prepared. Since the Health Assessment Document that the Subcommittee reviewed is a multimedia source document to meet Agency-wide needs, the health advisory was based on this information, updated in an appropriate way by a memorandum titled "quantification of toxicological effects." However, the support document distributed to the Subcommittee was the April, 1984, external review draft and not the September, 1985, final report and, as such, did not incorporate EPA's revisions in response to the Subcommittee's review. Certain of the Subcommittee's comments (below) repeat those in its previous report.

Overall, the health advisory generally is in agreement with the Health Assessment Document, which is appropriate data on which to base the advisory.

In the general information and properties section, the health advisory should note which uses of dichloroethane no longer occur. The rest of the uses should be divided into major and minor categories. The reader for whom the health advisory is intended can not be expected to supply this information, and information on obsolete uses may lead water works personnel to implicate sources which no longer exist.

Some physical properties (solubility, boiling point and density) cited in the health advisory are in conflict with those in the Health Assessment Document.

The sources of release of ethylene dichloride need to be clarified further. The data in the document indicate that the major release in air is from dispersive uses, such as lead scavenging, paint coating and adhesives. The health advisory indicates metal cleaning is the major source of release. Comments by the Chemical Manufacturers Association sent to the Subcommittee indicate that ethylene dichloride no longer is used for the above mentioned purposes.

In the section on pharmacokinetics, the qualitative statements about absorption are a representative summary of the information available, but the Subcommittee believes that a correlation between oral dose, inhalation dose and blood levels can be easily built. This will provide a better quantitative basis than the speculation in the health advisory based on physical and chemical properties. The absorption fraction of 30%, which is assumed in the calculations, needs a rationale, if retained in the light of the above comment.

ODW should modify the statements about distribution to indicate the amount of the dose which remains in the biological system at the termination of the distribution study. For example, this section might read as follows: "Within 48 hours after dosing, 96% of the administered radioactivity of a single oral dose of 150 mg/kg was

eliminated from the body in various metabolised forms." Distribution studies in these animals reveal that the liver and kidneys contained the highest concentration of the radioactivity. Reitz and coworkers showed that successively lower concentrations occurred in the forestomach, stomach and spleen.

Most information about "acute poisoning and toxicity" of humans in the health effects section originates from Russian studies. The Subcommittee has doubts about the veracity of these data, and the level of detail is skimpy. EPA should consider omitting these descriptions.

As opposed to the acute effects results for humans from the Russian literature, the Subcommittee suggests that the mutagenicity studies by Rappaport are credible.

The short term exposure data for animals are LD_{50}, not LD_{20} results.

Negative mutagenic activity of 1,2-dichloroethylene in Salmonella typhimurium was reported by McCann and coworkers in 1975.

The carcinogenicity bioassay data appear not to have been audited, and their validity may be in doubt. Deficiencies in the 1978 National Cancer Institute study were summarized in the comments presented to the Subcommittee by the Chemical Manufacturers' Association.

The Subcommittee argued in the previous Science Advisory Board report on ethylene dichloride that the structure-activity analogy with ethylene dibromide could be misleading in interpreting the metabolism of ethylene dichloride, especially in regard to possible reactive intermediates. However, a structure-activity analogy may be more appropriate in interpreting possible qualitative carcinogenic and mutagenic effects of ethylene dichloride than for metabolism.

In the section about quantification of toxicological effects, the units in the long-term health advisory should be ug/L, not mg/L.

If the Agency bases conclusions about pharmacokinetics on correlations between blood levels versus oral or inhalation doses, then a more reasonable basis will exist to use inhalational bioassay results.

E. DICHLOROETHYLENES [CIS-DICHLOROETHYLENE, TRANS-DICHLOROETHYLENE AND 1,1-DICHLOROETHYLENE (VINYLIDENE CHLORIDE)] HEALTH ADVISORIES

The information in the drinking water health advisories reflects the criteria documents for dichloroethylenes fairly accurately. All three advisories could be written better from the standpoint of more clearly delineating the differences between non-carcinogenic concentrations and that concentration which relates to carcinogenesis. These three health advisories should use wording similar to that found in the trichloroethylene advisory to distinguish acute from chronic toxicity.

In the sections about quantification of toxicological effects, the definitions of adverse effects for the three dichloroethylenes are inconsistent, as illustrated below:

> In the one day health advisory for cis-dichloroethylene, an elevated alkaline phosphatase is considered an adverse but not a life-threatening effect. In the trans-dichloroethylene one day health advisory, increased incidence of degeneration of the liver lobule and lipid accumulation by the Kupffer cells of the liver is not considered an adverse effect. In the one day health advisory for 1,1-dichloroethylene, a doubling of liver alkaline phosphatase and an 80% reduction in liver glucose-6-phosphatase is considered an adverse effect.
>
> In the longer term health advisory for 1,1-dichloroethylene, increased cytoplasmic vacuolization of hepatocytes in livers of both sexes is not considered an adverse effect. In the longer term health advisory for cis-dichloroethylene, an increased cytoplasmic vacuolization of hepatocytes is considered an adverse effect. In the longer term health advisory for trans-dichloroethylene, a trend towards increased fatty deposition in the liver was considered an adverse effect.

Vinylidene chloride may not be an appropriate toxicologic analog of the 1,2-dichloroethylenes. The Subcommittee has compared them, as follows:

1,2-Dichloroethylenes	Vinylidene chloride
Oral LD_{50} = 1300 mg/kg	Oral LD_{50} = 200 mg/kg
No observed effects at >1,000 ppm	Pathology seen at 10 ppm for 6 hours
Liver and kidney not affected	Liver and kidney affected
200 ppm TLV	5 ppm TLV
Not mutagenic in host-mediated *Salmonella* assay	Mutagenic for *Salmonella* with metabolic activation

A bioassay in *Salmonella* is not adequate mutagenicity testing. A computerized data base on this subject, such as that of the Environmental Mutagen Information Center, needs to be consulted.

COMMENTS SPECIFIC TO CIS-1,2-DICHLOROETHYLENE

The cis-dichloroethylene health advisory identified a no-observed-effect-level of 10 mg/kg, when the 5 mg/kg dose actually gave a decreased kidney to body weight ratio. If this decision was based on the absence of decreased kidney to body weight ratio at 10 mg/kg, a more complete description of the judgment is necessary.

In the longer term health advisory, a lowest-observed-adverse-effect-level is given for 100 ppm, rather than a no-observed-effect-level at 50 ppm.

If contaminated water is the main source of cis-1,2-dichloroethylene, why does the health advisory assume that drinking water supplies are only 20% of the exposure in the longer term health advisory?

In the pharmacokinetics section, almost all of the information is based on analogy. Therefore, some language changes seem desirable for the advisory to avoid confusing the reader. For example, the health advisory could state that "cis-dichloroethylene should be absorbed rapidly," or that "cis-dichloroethylene would be expected to be found in liver and kidney," or that "if similar to vinylidene chloride in excretion, then cis-dichloroethylene will be excreted relatively rapidly."

It is important to note in the health effects section that cis-dichloroethylene is well-tolerated as an anesthetic in man and animals, in addition to describing its anesthetic properties.

The subsection about health effects in animals reports that no data are available, but the American Conference of Government and Industrial Hygienists reports that no exposure related changes occurred from a mixture of 60% trans-dichloroethylene and 40% cis-dichloroethylene at 500 or 1000 ppm in rats, rabbits, guinea pigs, or dogs exposed for seven hours daily, five days each week for six months. Parameters studied included growth, mortality, organ and body weights, hematology, clinical chemistry, and gross and microscopic pathology.

In the section about other criteria, guidance and standards, the Threshold Limit Value (TLV) given is 200 ppm (790 ug/m^3). The health advisory states that, in view of the finding that the no-observed-effect-level in animals after prolonged inhalation is at least 1000 ppm, and the supporting information by other routes of administration, the TLV of 200 ppm and the short term exposure limit of 250 ppm may be too conservative. The Office of Drinking Water should note that 200 ppm is equivalent to 790 mg/m^3, 790 mg/m^3 x 10 m^3/day = 8,000 mg/day, and 8,000 mg/70 kg = 112 mg/kg/day. This suggests that the lifetime health advisory value, based on analogy to 1,1-diethylene, is too low.

The American Conference of Government Industrial Hygienists reports that liver and kidney injury do not appear to be important endpoints of cis-dichloroethylene exposure.

COMMENTS SPECIFIC TO TRANS-1,2-DICHLOROETHYLENE

The human health effects discussion does not decribe the experience of human exposures without adverse effects.

The subsection addressing effects in animals reports that the oral LD_{50} is 1/6th of intraperitoneal LD_{50}, which might suggest that a metabolite arises after the first pass that is responsible for the acute toxicity. If so, why does the advisory make a prediction of liver and kidney toxicity when no changes in organ weight were seen after 220 mg/kg by gavage for 14 days? Comparison of the inhalation data with the gavage study involves different endpoints, biochemical for the former and organ weight for the latter. If this difference is the basis of the choice of an inhalation study in preference to a gavage study, the health advisory needs to describe the rationale for the choice.

In the section about quantification of toxicological effects, an alternative derivation of the one-day drinking water health advisory based on inhalational data might be compared to the value of 2.7 mg/L in the health advisory, as follows: 200 ppm x 3.97 mg/m^3/ppm x 0.00438 m^3/hr/rat x 1 rat/0.190 kg x 8 hrs x 30% absorption x 10 kg child/Liter/day x 0.01 (uncertainty factor) = 43.8 mg/L

Some relevant papers were not cited in the reference section, such as that by Jenkins and coworkers (1976), and some were incomplete, such as those of Olsen and Gehring (1976) or Lehmann and coworkers (1936).

COMMENTS SPECIFIC TO VINYLIDENE CHLORIDE

In the reference section, a recent review of long-term studies in Environmental Health Perspectives and the Agency's Health Assessment Document on Vinylidene Chloride should be cited.

F. DICHLOROMETHANE (METHYLENE CHLORIDE) HEALTH ADVISORY

The support document for the health advisory is a final draft Criteria Document prepared by Life Systems, Inc., which is dated June, 1985. The Criteria Document represents another version of the more comprehensive Health Assessment Document, which was published by EPA in February of 1985, and the Addendum to the Health Assessment Document, which was published in August of 1985. Several articles and other information have appeared subsequently (cited below) that are pertinent to the health advisory, and this material should be incorporated into the health advisory.

EPA has received detailed comments from the Halogenated Solvents Industry Alliance on December 16, 1985 which focus on the carcinogenicity, non-carcinogenic health effects, exposure and risk assessment of dichloromethane (EPA/Docket No. OPTS-62045). At the same time, the Food and Drug Administration proposed in the Federal Register on December 17, 1985, to ban dichloromethane as an ingredient in all cosmetic products, citing studies showing that inhalation of the chemical causes cancer in rats and mice and poses a possible cancer risk to humans. The same notice did not propose a ban on use of dichloromethane in coffee decaffeination. The responses to both the EPA and FDA proposals need to be evaluated and used, as appropriate, in preparing the final versions of the health advisory and Criteria Document.

Some old business needs completing before the Criteria Document and health advisory are finalized. The health advisory merits revision on the basis that the data base is incomplete, as detailed below. The Criteria Document also is deficient and needs further detailed review or perhaps replacement by the Health Assessment Document and its Addendum. Specific comments include:

- In previous reports, the Science Advisory Board has requested that EPA provide sensitivity analyses of the Agency's risk estimates.

- EPA has decided to have an independent review of the Kodak epidemiology studies, which will be important to the Agency's reviews of available human data.

- EPA reviews of DNA-binding data submitted by the European Council of Chemical Manufacturer's Federation should be completed, if the Agency is to clarify the relative toxicity of the different dichloromethane reactive intermediates.

The health advisory and Criteria Document need to be reinterpreted in the light of the Agency's proposed guidelines for risk assessment, which the Science Advisory Board has reviewed, and which are operational within the Agency. Reinterpretation will be particularly important for dichloromethane with respect to benign versus malignant tumors and to weight of the evidence for carcinogenicity.

- The Agency's interpretation of the pharmacokinetics and comparative metabolism of dichloromethane needs additional peer review, particularly in regard to the use of this information in a risk assessment.

- An EPA report of May 1, 1984, authored by Cothern, Coniglio and Marcus, which assesses carcinogenic risk to populations from dichloromethane via the ingestion, inhalation and dermal routes, is not mentioned in the health advisory or Criteria Document.

In the section on general information and properties, add methylene bichloride under synonyms.

In the subsection about occurrence, the Subcommittee notes that the health advisory says that there are no natural sources, whereas the Criteria Document says that possibly there are natural sources. The question of potential natural sources may be important. The production figure in the health advisory appears to be more up to date than that in the Criteria Document. This conflict needs to be resolved. The remaining paragraphs in this subsection are presented as categorical statements of fact with no references cited; neither is any information provided in the Criteria Document. This needs to be corrected so that data are available to support the statements, judgments, assumptions, and uncertainties in this section.

In the section about pharmacokinetics the most recent pharmacokinetics and comparative metabolic data relative to the interpretation of the findings on the animal studies need to be reviewed in detail by the EPA. In response to the October 17, 1985 Advanced Notice of Proposed Rulemaking, EPA has received comments and new experimental data. In addition to the Halogenated Solvents Industry Alliance comments mentioned previously, EPA has received detailed information (including two publications and five preprint manuscripts) from the National Coffee Association. These papers present pharmacokinetic modelling of data from orally administered dichloromethane to rats and mice. (EPA Docket No. OPTS-62045).

In the health effects section, two drinking water studies are mentioned under long-term exposure, but there is no reference to the Dow chronic inhalation studies. This is also true of the Criteria Document. The Office of Drinking Water draft issue paper by K. Khanna ("Use of Inhalation Data for Estimating Acceptable Exposure Levels in Drinkng Water," September 12, 1985) explains the validity of extrapolating from inhalation to oral exposure. The Dow studies may, therefore, be useful.

The subsection on teratogenic/reproductive effects should be revised to emphasize that the studies were not dose-response designs and that high doses were tested. Furthermore, EPA has received a copy of a report by Nitschke, Eisenbrandt, and Lomox (1985), which describes negative results in a two-generation inhalation study in Fischer 344 rats.

In the National Coffee Association submission, a detailed review by Broome and Sivak of mutagenicity data on dichloromethane is included. This paper suggests that a genetic rational for a carcinogen risk assessment of dichloromethane is inappropriate. EPA should examine this paper and evaluate the assertions made.

Reference to the National Toxicology Program chronic oral study should be deleted in the carcinogencity subsection since the Board of Scientific Counselors has disavowed this study with respect to providing background information on the forthcoming publication of their inhalation study. The pertinent sections in the Criteria Document (pages V-28-V-30 and V-40-V-41) should likewise be deleted.

The carcinogenicity subsection contains a detailed summary of the Hazelton Laboratories chronic drinking water bioassay. However, page six of the health advisory states that EPA (1985) performed an independent assessment of the data from this study and concluded that "the 250 ng/kg/day dose was borderline for carcinogenicity in Fischer 344 rats." No details of that assessment are provided in either the text of the health advisory or the Criteria Document, and there is no 1985 citation given in the References section. The reasons for this conclusion should be presented before the reader can understand the overall interpretation.

In the carcinogenicity subsection, EPA accepts the National Toxicology Program two-year inhalation data to provide evidence of carcinogenicity. The same studies, however, are not mentioned in the advisory for longer-term exposure. Perhaps, the Agency needs to combine the two subsections for longer-term exposure and carcinogenicity into one.

The human exposure section of the Criteria Document was unavailable for review and comment.

The section on quantification of toxicological effects presents health advisories for a 10 kg child exposed for one day or for ten days. Health advisories are missing for 70 kg adults exposed for one day or ten days. These calculations are included in the Criteria Document and should be included in the health advisory. Also missing from both the health advisory and Criteria Document is a calculation of a longer-term exposure health advisory. It is stated that no data were available for the calculation. EPA needs to reexamine the literature and make the calculations.

Concerning the evaluation and calculation of carcinogenic potential, the National Toxicology Program chronic oral study should be deleted from the data base, and this section should be reworked because the study has not been accepted by the National Toxicology Program Board of Scientific Counselors. The lifetime health advisory should be placed into context with levels of dichloromethane in water and other environmental media. Perhaps the Advanced Notice of Proposed Rulemaking will provide this perspective.

G. 1,2-DICHLOROPROPANE HEALTH ADVISORY

The health advisory contains information that is not provided in the Criteria Document. The quality of the Criteria Document needs to be upgraded to contain the missing information.

In the section about general information and properties, the information about occurrence is not found in the Criteria Document.

The Criteria Document contains no information on the extent of absorption. The statement that "90% of the orally administered dose is absorbed" lacks justification.

The metabolism information provided in the advisory is misleading. The study described by Jones and Gibson (1980) indicates that two metabolites represent only 25-35% of the administered dose. Structures and contributions of other potential metabolites were not determined.

The human health effects information provided in the health advisory is not accurate and was presented with no details. For example, one abstract was cited as describing the toxicity of a cleaning substance which contained substances other than dichloropropane.

In the section about quantification of toxicological effects, the ten day health advisory is based mainly on information from two Russian abstracts. Because the experimental design, data and results are questionable, EPA's conclusions based on this information may be in some doubt.

In the reference section (literature citations), National Toxicology Program (1983) information is available in the Criteria Document. However, the information provided on this report may change pending auditing of the experimental data and issuance of final report by National Toxicology Program. Is this final report available?

H. 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN HEALTH ADVISORY

There is a relatively good correspondence between the data and conclusions presented in both the health advisory and Criteria Document for 2,3,7,8-tetrachlorodibenzo-p-dioxin. However, there is one important consideration which has not been addressed in either document: the problem of human exposure not only to 2,3,7,8--tetrachlorodibenzo-p-dioxin (TCDD) but to other polychlorinated dibenzofuran (PCDF) and dibenzo-p-dioxin (PCDD) isomers and congeners. Recent studies by Rappe and coworkers, and others, have demonstrated that a number of highly toxic PCDDs and PCDFs bioaccumulate in human adipose tissue (Chemosphere 14: 933, 1985; Chemosphere 14: 697, 1985) and in most cases, TCDD is a minor component of these toxic mixtures. There are several studies that demonstrate the value of using "tetrachlorodibenzo-p-dioxin equivalents" for describing the potential adverse human and environmental health effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds, and this concept should be noted in the health advisory. It is likely that in the future there will be an increase in the number of reports which confirm the presence of other toxic PCDDs and PCDFs in humans, and it would be prudent to recognize this possibility in both documents.

The Uses section should be retitled Uses and Occurrence, and this section should note identification of TCDD in fly ash as a by-product of combustion.

The formula of TCDD should be properly drawn.

The Pharmacokinetics section should include recent studies which have identified 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in human tissues (Chemosphere 14: 697, 1985; Chemosphere 14: 933, 1985).

The metabolism section should note that the metabolite profiles are consistent with an arene oxide intermediate. The covalent interaction of TCDD with cellular macromolecules is minimal. A statement like this would summarize the likely route of oxidative metabolism and also point out that covalent modification of DNA, RNA and protein is not significant.

Although TCDD is a mouse teratogen it is not "teratogenic in all strains of mice tested." A study by Poland and Glover (Mol. Pharmacol. 17: 86, 1980) reported that at a dose level of 30 ug/kg the CBA/J, AKR/J, SWR/J and 129/J strains were resistant to the teratogenic effects of TCDD.

TCDD is fetotoxic and a reproductive toxin in rats, but it is not generally regarded as rat teratogen.

While the Criteria Document is well written and provides supporting evidence for the health advisory, there are a number of sections which merit modification. Detailed comments on some recommended changes have been sent directly to the Office of Drinking Water by individual Subcommittee members.

I. EPICHLOROHYDRIN HEALTH ADVISORY

The ten day drinking water health advisory for a child is 0.14 mg/kg/day (or other equivalent), and the lifetime drinking water health advisory (and/or DWEL) for an adult is 0.15 mg/day. These values appear inconsistent, perhaps due to an error in accounting for body weight, and merit additional comment in the advisory.

Is there a consistent carcinogen risk policy? Is a risk of approximately 2×10^{-5} an acceptable EPA upper limit of risk? While de facto risk may be orders of magnitude lower than the stated value, what is the rationale for this maximum risk value for epichlorohydrin?

Synonyms should be checked with the Criteria Document and the Epichlorohydrin Health Assessement Document Final Report. For example, chloromethyl oxirane is not listed there, but chloromethyl ethylene oxide is.

A vapor pressure of 12 mm at 20°C is given, but a pressure of 10 mm at 16.6°C and 22 mm at 30°C appears in EPA's final report.

In the section on mutagenicity, the Subcommittee suggests that the fourth sentence read as follows: "Epichlorohydrin also induces gene mutations and very likely chromosomal aberrations in mouse cell culture studies (Moore-Brown and Clive, 1979) and chromosome breakage in human lymphocytes in vitro (Keicerova and coworkers, 1976)."

Through in vivo studies, Sram (1976) demonstrated a clear dose-response relationship in mouse bone marrow studies.

A study by Laskin was used to set the DWEL. Tumors occurred after six weeks, and their incidence suggests a dose-response relationship.

A separate section on organoleptic properties would make the health advisory more useful.

J. HEXACHLOROBENZENE HEALTH ADVISORY

In the section about general information and properties, it is worth noting that hexachlorobenzene has an extremely low water solubility of 5 ug/l (not 0.05 mg/l).

Hexachlorobenzene has no natural sources. Use of hexachlorobenzene as a fungicide has been discontinued. Hexachlorobenzene is a contaminant of some pesticides. The low water solubility implies rapid partition to soil following releases to the environment with a half-life of 3-6 years. Hexachlorobenzene bioaccumulates in fish. It has been detected at 0.005 ug/L in two drinking water supplies and in some foods at ppb levels. Diet probably is the major route of exposure.

In the pharmacokinetics section, gastrointestinal absorption of hexachlorobenzene occurs primarily through lymphatic channels, which route is dependent on solvent vehicle. In olive oil, 80% is absorbed; in aqueous solution, less than 20%. This difference is not accounted for in the calculations, so the health advisory will overestimate the internal exposure via drinking water.

Hexachlorobenzene is lipophilic, accumulates in adipose tissues and crosses the placenta.

Hexachlorobenzene undergoes slow metabolism, with the parent compound excreted in feces (more than 90% of dose) and the metabolites in urine.

In the health effects section, it should be noted that exposure of humans in Turkey occurred via consumption of contaminated wheat seed.

A more specific description of the human effects in the Turkish episode would be desirable. For example, very high mortality (95%) occurred in children under 1 year of age. The "few" patients quoted in the health advisory actually was 15/161, almost 10%; the greater than 50% actually was 78% hyperpigmentation, 83% scarring. Thyroid enlargement in 60% of the exposed females is not mentioned. In the Criteria Document, thyroid tumors in 60% of females are described. Hexachlorobenzene also causes hypothyroidism in animals (Rozman and coworkers, "Reduced Serum Thyroid Hormone Levels in Hexachlorobenzene Induced Porphyria," Toxicology Letters 30: 71-78 [1986]).

Both the health advisory and the criteria document report significant increases in liver and kidney weights in several species of treated animals. But Table V-1 and the rest of the subchronic toxicity section indicates an effect on kidney weights only in rats. Has the Criteria Document been checked for internal consistency?

Increased mortality plus hepatic and renal lesions occur in rodents. Histopathologic effects occur in monkey ovaries. The most prominent effect is increased porphyrin levels in liver and urine, to which females are more sensitive than males. Hexachlorobenzene causes

accumulation of beta-H-steroids (not para-H-steroids), which induce porphyrin synthesis. Pentachlorophenol, a hexachlorobenzene metabolite (but not hexachlorobenzene itself) inhibits uroporphyrinogen decarboyxlases, but only above 10^{-5} M. Hexachlorobenzene also induces cytochromes and hepatic microsomal enzymes.

Hexachlorobenzene occurs in the milk of nursing dams. Reduced fertility, litter size, hepatomegaly and compromised survival of pups occur on exposure. Developmental effects, such as cleft palate, occur in mice but not rats.

Hexachlorobenzene is not mutagenic in Salmonella strains with or without metabolic activation, does not induce dominant lethal mutations in rats, but is mutagenic in yeast.

Hexachlorobenzene is carcinogenic in hamsters, rats, and mice. Most often liver tumors occur, with some adrenal, kidney, thyroid, and parathyroid tumors. The study of Lambrecht and coworkers (1983) is only mentioned in this section, although it is the data set used by EPA to estimate carcinogenic potency.

In the section about quantification of toxicological effects, diets with hexachlorobenzene in corn oil probably overestimate internal dose versus equivalent exposure in drinking water. A no-observed--adverse-effect-level of 0.6 mg/kg/day was found for female rats (a transient increase in liver porphyrin levels four weeks after removal of hexachlorobenzene). Higher doses yielded increased porphyrin levels in liver, kidney and spleen; increased liver to body weight ratios, decreased survival, and so forth. Ten-day drinking water health advisories for child and adult are 50 and 175 ug/L, respectively, which are 10 and 35 times higher than hexachlorobenzene solubility in water.

Based on the study by Arnold and coworkers in 1983, in utero exposure followed at 28 days by dietary exposure at parental levels for 130 weeks, the health advisory derives a no-observed-effect-level of 0.32 ppm. Periportal glycogen depletion occurred, only in F1 generation males at 1.6 ppm, so 1.6 ppm also can be observed as a no-observed-effect-level. At 8 ppm and higher exposures, hexachlorobenzene resulted in increased hepatic centrilobular basophilic chromogenesis, pup morbidity, peribiliary lympocytosis and fibrosis, severe chronic nephrosis in males, adrenal pheochromocytomas in females and parathryoid tumors in males.

One and six-tenths ppm equals 0.08 mg/kg/day on average, which also yields an adult DWEL of 28 ug/L, the same value as the lifetime acceptable daily intake given in the criteria document. This value is more than five times greater than the solubility of hexachlorobenzene in water.

K. POLYCHLORINATED BIPHENYLS HEALTH ADVISORY

The pharmacokinetics discussion should broadly summarize the data on polychlorinated biphenyls. This section focuses primarily on results from a single paper and is not representative of the facts. The draft health advisory for polychlorinated biphenyls also is inconsistent with the Criteria Document. The section on excretion is an example. The health advisory states that no data were available. It would seem that the major elimination pathway through urine could be inferred from the 1975 data of Yoshimura and Yamamoto, which are quoted in the Criteria Document and which show small percentages of polychlorinated biphenyls excreted in the feces. This inference is supported by two other studies cited in the Criteria Document which report that excretion of specific polychlorinated biphenyls occurs increasingly in the feces as the degree of chlorination of the biphenyl portion of the molecule increased (and as metabolism presumably was increasingly inhibited). In addition, several studies that are cited as dealing with polychlorinated biphenyl metabolites found a negative correlation between rapid urinary excretion and degree of chlorination of the mono- through hexa-chloro isomers. Matthews and Anderson also found that excretion half-life appeared to be negatively correlated with increasing chlorination. Other investigators, such as Muehlebach and Bickel, have reported half--life data. Felt and coworkers (1977) reported polychlorinated biphenyl elimination rates in rhesus monkeys, and Chen and coworkers reported similar data for humans. These studies are summarized in the Criteria Document.

The brief discussion of metabolism is incomplete. This section should note the importance of (a) degree of ring chlorination, (b) substituent orientation and (c) the availability of adjacent unsubstituted carbon atoms.

In the section on short-term exposure, depending on what was meant by "asymetrical skull" and taking into consideration other factors, such as the developmental stage at the time of abortion, such a finding in aborted fetuses may have little toxicological significance.

The discussion of effects of short term exposure to polychlorinated biphenyls on the immune system does not correspond with that found in the Criteria Document. The specific references, findings, timing, doses at which a response was seen, and so forth, differ between the health advisory and the criteria document.

In the analysis of data from Allen and coworkers, although it is true that the menstrual cycles were irregular and serum levels of sex steroids were depressed, the monkeys had "extreme weight loss." Therefore, the hormonal problems may have occurred secondarily to other toxic effects.

The useage of "isomers" and "cogeners" should be corrected. Polychlorinated biphenyls are not mixtures of isomers but mixtures of isomers and congeners.

The health effects section suggests that the short-term human exposure of Yusho poisoning is representative of polychlorinated biphenyl toxicosis. Recent studies indicate that the major etiologic agents in Yusho were polychlorinated dibenzofurans rather than polychlorinated biphenyls.

At least three papers have reported the immunotoxicity of several polychlorinated biphenyl isomers and congeners (Clark et al, Immunopharmacol. 6: 143, 1983, Silkworth et al, Toxicol. Appl. Pharmacol. 65: 109, 1982 and 75: 156, 1984).

The analysis section is out of date. It is possible to analyse polychlorinated biphenyls by congener-specific capillary gas chromatography using all 209 polychlorinated biphenyls as standards. This procedure will eliminate the guessing from future polychlorinated biphenyl analytical methods and ultimately will permit risk assessment to be based on individual compounds that are present.

EPA needs a source document for polychlorinated biphenyls. The Subcommittee has provided detailed scientific comments on the Drinking Water Criteria Document for Polychlorinated Biphenyls to the Office of Drinking Water, which included thirty major comments and thirteen minor comments. The final draft of the Criteria Document gives a date of March, 1985; whereas the document is out-of-date. The data and papers which are included and some of the interpretations are highly inadequate. Some of the issues have not been thoroughly discussed. In view of the comments below, the Subcommittee strongly recommends that the Drinking Water Criteria Document for Polychlorinated Biphenyls be extensively revised and updated. Specific comments include:

- Recent papers indicate that Yusho poisoning is primarily related to the toxic polychlorinated dibenzofurans and not the polychlorinated dioxins in contaminated rice oil. Thus, a discussion of the human health effects of polychlorinated biphenyls should not use "Yusho" as an example. Industrial exposure data more accurately reflect human health effects.

- The discussion of chemical analysis of polychlorinated biphenyls and the complexity of polychlorinated biphenyl mixtures is out of date, and any revised document should recognize important new advances in this field.

- A multitude of important papers on structure-activity relationships for polychlorinated biphenyls have been published but are not cited in the document. For polychlorinated biphenyls, this is a critical issue which must be thoroughly discussed.

- The mechanism of action of polychlorinated biphenyls has been extensively reviewed but is not covered adequately in the Criteria Document. [See, for example, CRC Crit. Rev. Tox. 13: 319 (1985), Environ. Health. Perspect. 60: 47 (1985) or Environ. Health. Perspect. 61: 21 (1985)]. These sections of the Criteria Document are out of date and need revision.

L. TETRACHLOROETHYLENE HEALTH ADVISORY

The health advisory states that the major sources of exposure to perchloroethylene result from contaminated water and to a lesser extent, air. The Agency's Health Assessment Document states the opposite. The idea that a main source exists in comparison to a secondary source may be misleading.

Some health advisory statements are potentially misleading, such as: "the accumulated human inhalation data indicate that there is a minimal effect on motor coordination at 100 ppm". The time frame is omitted. Similarly, the exposure range at which inebriation first appears is 300-475 ppm, and effects appear to vary with the time of prior exposure. This perspective is more informative than simply noting that inebriation is seen. A related problem occasionally occurs when abbreviated statements of fact are made. For example, in describing the distribution of perchloroethylene, the health advisory states "in rats," whereas a better description might be "in rats previously exposed to perchloroethylene by inhalation at 1340 mg/m^3 for 6 hrs/day and 4 days, the perchloroethylene concentration on the fifth day is highest in perirenal fat. Exposure to the same perchloroethylene concentration on the sixth day showed that..."

When such terms as SGOT are used as a measure of toxicity, information on the relationship to liver damage should be included. Most readers will not know the significance of increased serum SGOT.

Some other synonyms could be added, such as ethylene tetrachloride, Nema, Tetracap, Tetropil, Perclene, Ankilostin, Didakene.

The properties section should note that perchloroethylene is a colorless liquid. For specific gravity, add a superscript of 15 and a subscript of 4. Also, the document should note that the partition coefficient (water/air) is 1.22 ($20^{o}C$), that perchloroethylene is nonflammable, and that the odor threshold in water is 50-300 ug/l.

The health advisory should note that perchloroethylene degrades in the presence of sunlight and moisture.

If degradation to trichloroethylene and vinyl chloride is not a usual route, then the conditions, such as laboratory rather than ambient, should be discussed or the reference should be omitted.

The health advisory should include the annual production of perchloroethylene.

The section on absorption should note that ninety-eight percent of a single oral dose of 189 mg/kg perchloroethylene administered to rats was excreted in expired air (Daniel, 1963). In mice given a single oral dose of 500 mg/kg ^{14}C-labeled perchoroethylene, approximately 85% was recovered in expired air with total recovery of 96.8% in 72 hours (Schumann and coworkers, 1980).

The 25% perchloroethylene absorption figure given for humans in the health advisory does not appear in the Criteria Document. The health advisory states that 25% of inhaled perchloroethylene was absorbed during a four-hour exposure at 72 or 144 ppm. Also, the description of exposure as "72 to 144" ppm implies a variable exposure within a range, whereas the actual conditions were either 72 or 144 ppm exposure.

The Subcommittee has general concerns about the assumption of values for absorption fractions without clearly stating when they are based on reference studies and when they constitute arbitrary assumptions. For perchoroethylene, the 50% value contrasts with the values assumed for other substances, like trichloroethylene, for which a 35% value is used. Perhaps a better systematic approach is to base the values on physical solubility measurements.

The statement about three distinct half-times for perchloroethylene exhalation need clarification and amplification.

The health advisory needs a more extensive description of saturation kinetics of perchloroethylene and the implications of saturation kinetics. It also may be useful to cite recent studies about protein binding of metabolites.

The health advisory should note that trichloroethanol is a human metabolite of perchloroethylene because trichloroethanol is thought to be the active metabolite in some of the hypothetical mechanisms proposed for perchloroethylene effects.

The discussion of the "proposed metabolic pathway" is incorrect. This sentence should state that oxidative metabolism is proposed to proceed through an epoxide intermediate, which can lead to the major metabolite, trichloroacetic acid.

The problem with some of the effects data is that the length of exposure was quite variable. In the study of Rowe and coworkers (1952), effects are associated with a single exposure ranging in time from two minutes to two hours. The study of Stewart and coworkers (1961) noted an impaired ability to maintain a normal Romberg test after a 30-minute exposure of volunteers to 190 ppm. Either the second paragraph is misleading or else these studies should be included as short-term effects. The study of Stewart and coworkers (1970) involved exposures of 7 hours per day for 5 days. In 1974 Stewart's group also exposed 19 volunteers to perchloroethylene at 20 to 150 ppm for a 5 week period and noted deleterious effects at 100 ppm but not at 20 ppm. These data provide a basis for a 10-day advisory.

Results of the study of Schwetz and coworkers (1975) were characterized by fetotoxicity, not developmental effects, and these results would be better placed in the health effects section.

The Subcommittee does not have a general consensus about the use of develpmental toxicity data in which maternal toxicity is observed. However, current EPA practice is to use effects information at an exposure for which less than 10% maternal mortality is observed. Obtaining maternal mortality at the highest dose in such studies is not considered inappropriate. ODW should consider performing a comprehensive re-evaluation of the literature on the developmental toxicity of perchloroethylene.

The carcinogenicity section should be updated to include the papers by Van Duuren and coworkers (See J. Natl. Cancer Inst. 63: 1433, 1979). Moreover, a recent paper by this group (Cancer Res. 43: 159, 1983) reports the carcinogenicity of chloroalkene oxides and their parent olefins after topical or subcutaneous administration. Perchloroethylene oxide, presumably the metabolically activated perchloroethylene metabolite, did not significantly increase tumor incidence after subcutaneous injection but did produce benign skin tumors in mice at a low frequency.

The route of administration, dose (or doses), purity, and target organs or tissues should be stated in describing the chronic studies for perchloroethylene.

National Cancer Institute chronic bioassay data suggest that perchloroethylene may be acting as a carcinogenic promoter. The Dow Chemical Study by Rampy and coworkers (1978) merits some mention in the drinking water health advisory. Perhaps it was excluded because it was an inhalation study. However, the results in Sprague-Dawley Spartan substrain rats were negative and can be useful in placing limits on the risk estimates.

In calculating the total absorbed dose, the conversion of a 5-day exposure to a 10-day exposure was omitted.

A recommendation to the public of boiling water to remove perchloroethylene seems dubious, unless it is made clear that the water is to be boiled outdoors.

The Subcommittee suggests that the key to interconverting bioassay data for perchloroethylene administered by different routes of administration is to correlate blood levels with exposure (or dose) for different species. Sufficient data is available for perchloroethylene, including humans, to adopt this approach.

M. 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM) HEALTH ADVISORY

With the exceptions described below, the drinking water health advisory is generally consistent with the information presented in the Criteria Document.

The drinking water health advisory states that the major source of methyl chloroform results from its use as a metal degreaser. Entrance to the environment is from evaporation and dumping of the grease contaminated chemical into landfills, open ground or sewers. Due to the costs of methyl chloroform and changes in environmental standards, most methyl chloroform is recovered and recycled. Although the evaporation problem continues, current disposal practices are probably not contributing to ground water levels at this time. Much of the existing ground water problem is apparently due to past practices. The drinking water health advisory also states that the major source of human exposure is through the water supply and, to a lesser extent, air. There is no clear indication of source predominance for methyl chloroform on a site-by-site basis. According to the Criteria Document, exposure in water predominates over air only at drinking water levels above 84 ug/L, which are levels to which less than 0.1% of the population are exposed.

The 1,1,1-TCE abbreviation might be changed to avoid confusion with trichloroethylene, or else use the synonym "methyl chloroform" as in the present comments.

The discussion of pharmacokinetics lacks data on the elimination rate. Although the Criteria Document does not present a half-life after acute exposure, 44% of an inhaled dose is excreted within one hour, suggesting a short half-life, but these data receive little attention. There is the possibility of accumulation in tissue during chronic exposure, with one study showing trace amounts of methyl chloroform still present one month after chronic exposure.

There is an apparent error in referring to the study of Monster and coworkers (1979), where the health advisory states that very small amounts of methyl chloroform are excreted unchanged by the lungs. Although lung excretion will depend on dose, the lungs are the major route, with the parent compound accounting for almost all of the excretion. Perhaps the health advisory is referring to the metabolic product, trichloroethanol, which accounts for less than 1% of the total dose of methyl chloroform administered.

The study by Hake and coworkers (1960) suggests that about 3% of methyl chloroform is metabolized by rats. Actually this study showed that 98% of the radioactivity was associated with the unchanged compound and 0.5% as $^{14}CO_2$. About 50% of the remainder was associated with metabolites, while the other 50% was lost to evaporation. Thus, less than 1% was metabolized.

The description of the human data needs expansion. A concentration (68 mg/L) producing death by central nervous system depression is known. The sensitization of the heart to catecholamines and the sudden deaths due to the cardiovascular effects of methyl chloroform are not mentioned. Central nervous system functional impairment has been demonstrated with concentrations of methyl chloroform as low as 250 ppm in air. Upper respiratory irritation and the unpleasant odor also observed at low concentrations are not mentioned.

The study by Vainio and coworkers (1976) should be placed in perspective. The 1.4 g/kg dose that depressed microsomal metabolism is about 25% of the LD_{50} and well above the dose that induces anesthesia.

A 1983 National Toxicology Program is presented, but the results of the study are not discussed.

The health advisory uses the studies of McNutt and coworkers (1975) to calculate a lifetime advisory of 200 ug/L. The health advisory uses a lowest-observed-adverse-effect-level of 250 ppm for mice and values for humans into the appropriate formula. If, instead, mouse body weight and ventilation rate are taken into consideration, a 10-fold higher advisory will result.

Skin absorption is not considered in detail. There is some skin absorption with methyl chloroform, but it does not appear to be a major contributor to exposure, based on data in the Criteria Document.

There is considerable data available on human toxicity of methyl chloroform, but little of this data is mentioned in the health advisory.

The analysis of mutagenicity results needs further clarification with respect to the actual material tested, presence of contaminants, and so forth. In particular, the analysis should consider the possibility of action on spindle fibers and resulting clastogenic action.

If methyl chloroform is classified under EPA's new guidelines as a category D carcinogen, the health advisory should not refer to a q_1^* for carcinogenic potency.

The health advisory should reference and consider two potentially confusing aspects: (1) the 1-day advisory is approximately the same as the advisory for "longer-term" adult exposure, and (2) the solubility of methyl chloroform in water is less than the advisory levels. Further explanation of these apparent inconsistencies is desirable.

N. 1,1,2-TRICHLOROETHYLENE HEALTH ADVISORY

In general, the information in the drinking water health advisory for trichloroethylene accurately reflects the criteria document. The health advisory for tricholoroethylene more clearly delineates the differences between non-carcinogenic concentrations and the concentration which relates to carcinogenesis than do other advisories. However, the trichloroethylene health advisory does not use the Criteria Document for trichloroethylene for all the source material. In many cases, the drinking water health advisory material cited is more recent than that cited in the Criteria Document.

In the section about general information and properties, some other synonyms for trichloroethylene could be added, such as ethinyl trichloride; Tri-Clene; Trielene; Trilene; Trichloran; Trichloren; Algylen; Trimar; Triline; Tri; Trethylen; Trethylene; Westrosol; Chlorylen; Gemalgene; Germalgene.

The description of physical properties is not complete, and the Subcommittee suggests adding the following additional information, which may be of value and which was obtained from Patty's Industrial Hygiene and Toxicology (Vol. IIB, 1981).

Vapor Pressure	75 mm Hg (25°C)
Water Solubility	0.1g/100 ml(H_2O, 20°C)
Boiling Point	8.7°C (760 mm Hg)
Density	1.456 (25°C)
Physical State	Colorless Liquid
Nonflammable	
Autoignition Temperature	410°C
CAS #	79-01-6.
% in Saturated Air	10.2 (25°C)
Conversion Factors	1 ppm in air = 5.38 mg/m^3 at 25°C, 760 mm Hg
	1 mg/L = 185.8 ppm

According to the comments received by the Subcommittee, trichloroethylene is generally recovered from degreasing residues and recycled, while the dumping of trichloroethylene on the ground has been prohibited. Thus, contamination of ground water is likely to be a result of past disposal practices. The health advisory should state whether the Agency agrees with these comments.

Trichloroethylene is degraded in the presence of light and moisture.

The section about pharmacokinetics should note that after excretion in human urine, Soucek and Vlachova (1959) reported the ratio of trichloroethylene metabolites to be 1:5:12 (monochloroacetic acid: trichloroacetic acid: trichloroethanol). More recent studies with humans are reported in the Criteria Document, although results are similar. Based on total trichlorocompounds in the urine of factory

workers, the biological half-life of trichloroethylene was calculated to be approximately 41 hours (Ikeda and Imamura, 1973). Trichloroethylene does not bioaccumulate.

Acute exposure to trichloroethylene is associated with liver damage and cardiac irregularities. After longer exposures, the most common complaints of exposed workers involve central nervous system disturbances.

Inhaled trichloroethylene (500 ppm) depressed myocardial activity in dogs (Aviado and coworkers, 1976).

The health advisory should note that Tucker and coworkers (1982) found that pale, spotty and granular livers developed in all groups of male and female mice exposed for six months to trichloroethylene in drinking water at 100, 1,000, 2,500 and 5,000 mg/L.

The health advisory does not describe developmental effects bioassays in which no positive results were found, or summarize any of the information about reproductive effects. For example, Zenick and coworkers (1984) found no trichloroethylene-related effects on the sperm of male rats after oral administration, and Manson and coworkers (1984) found no fertility and pregnancy effects in female rats. Reproductive effects were not found in four epidemiology studies.

The health advisory omits reference to a 1980 National Cancer Institute bioassay. Doses of trichloroethylene should be listed for all carcinogenicity studies.

The study by Kimmerle and Eben (1973) does provide a reasonable basis for the calculation of a DWEL, but it should be noted that increased liver weight was found after 14 weeks exposure (5 days/wk) to 55 ppm by inhalation, which indicates a toxic response in the liver. The advisory might report the number of animals per group, effects on body weight, and any other endpoints that were reported by Kimmerle and Eben.

The RRfD value reflects a calculational error.

The Subcommittee recommends that Agency staff carefully review the available chronic bioassay data for possible pathological changes, such as organ weight changes, that could be used to calculate effects levels.

O. VINYL CHLORIDE HEALTH ADVISORY

The health advisory and the Criteria Document contradict each other about population exposures. The health advisory states that little or no exposure is expected from food, whereas the Criteria Document states that the principal source of vinyl chloride exposure for most Americans is probably from polyvinyl chloride food containers, which contribute approximately 1 ppb to the diet.

The difference in ^{14}C-vinyl chloride distribution between the study by Bolt and coworkers (1976) compared to those of Watanabe and coworkers (1976a,b) is not a time difference in distribution but a difference in the time of ^{14}C assay after administration of the labeled compound (72 hours post-administration compared to immediately). The Bolt article is also misquoted.

The information about the model of Withey and Collins (1976) relates to absorption instead of excretion.

In the section about human health effects, the actual exposure conditions of 40-900 ppm in air should be cited, rather than describe them as "high." These values might be compared to the U.S. Occupation Safety and Health Administration standard of 1 ppm.

The description of carcinogenic effects should be placed in the section on human health effects, should refer to Tabershaw and Gaffey (Journal of Occupational Medicine, 1979) and should begin with note on the work of Creech and Johnson (Journal of Occupational Medicine, 1974). It may be worthwhile to point out the high risk and specificity of association with a rare tumor.

Although the studies by Infante on birth defects have been in dispute, they should be mentioned. Dominant lethal studies have been negative, as reported by Purchase and coworkers (Lancet, 28: 410, 1975).

The health advisory describes the data of Torkelson and coworkers (1960) as a 7 hour daily exposure, but the Criteria Document describes the same study as a 2 hour daily exposure. If the latter value is correct, a difference of 3.5 is introduced into the calculation of the 10-day advisory. A 10-day advisory also could be calculated from the inhalation study of Torkelson and coworkers (1961), using the calculation of Withers and Collins (1976), as follows:

$$100\text{ppm} \times \frac{7}{24} \times \frac{5}{7} \times \frac{20\text{mg/L}}{2\text{ ppm}} \times \frac{40\text{ml/day/rat}}{250\text{ gram/rat}} = 33\text{ mg/kg/day}$$

The data of Feron (1981) and Til (1983) are misdescribed. Feron found no angiosarcomas at 1.7 mg/kg/day and at 5 mg/kg/day found a significant excess of angiosarcomas in male rats and a significant excess of hepatocellular cancers in female rats. Til found no significant excess of hepatocellular cancer at 1.7 mg/kg/day in female rats, but did in males. Til also found a nonsignificant increase in the incidence of angiosarcoma at 1.7 mg/kg/day for either sex of rat.

The data of both studies can be summarized, as follows:

Male Effects	Data of Til (1983)				
Dose	0	0	0.017	0.17	1.7
Basophilic Foci	5	16	12	15	23
Neoplastic Nodule	0	0	0	0	3
Hepatocellular Cancer	0	0	0	0	3
Angiosarcoma	0	0	0	0	1

Male Effects	Data of Feron (1981)			
Dose	0	.....	1.7	5	14.1
Basophilic Foci	8	.....	18	21	22
Neoplastic Nodule	0	.....	1	7	23
Hepatocellular Cancer	0	.....	1	2	8
Angiosarcoma	0	.....	0	6	27

Female Effects	Data of Til (1983)				
Dose	0	0	0.017	0.17	1.7
Basophilic Foci	19	7	17	31	32
Neoplastic Nodule	0	0	1	1	10
Hepatocellular Cancer	1	0	0	1	3
Angiosarcoma	0	0	0	0	2

Female Effects	Data of Feron (1981)			
Dose	0	.....	1.7	5	14.1
Basophilic Foci	2	.....	33	17	28
Neoplastic Nodule	0	.....	26	39	44
Hepatocellular Cancer	0	.....	4	19	29
Angiosarcoma	0	.....	0	2	9

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
January 14-17, 1986

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Executive Secretary

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COMMENTS SUBMITTED TO THE HALOGENATED ORGANICS SUBCOMMITTEE

BY MEMBERS OF THE PUBLIC REGARDING THE REVIEW OF

DRAFT DRINKING WATER HEALTH ADVISORIES

National Audubon Society
National Capital Office
645 Pennsylvania Avenue, S.E.
Washington, D.C. 20003

Contact: Chuck Pace

Date: December 24, 1985

Chemical Manufacturers Assoc.
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Contact: Geraldine V. Cox

Date: December 26, 1986

Natural Resources Defense
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Contact: Robin Whyatt
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Date: November 29, 1986

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Contact: Danna M. Cirolia

Date: November 22, 1985

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Contact: Paul A. Cammer

Date: December 9, 1986

Diamond Shamrock Corporation
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Contact: Ross E. Jones

Date: December 2, 1985

The Society of the Plastics Industry, Inc.
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Contact: Hugh Toner

Date: December 16, 1985

The New Jersey Dept. of Health
and The New Jersey Dept. of
Environmental Protection

Contact Bonnie L. Bishop

Date: August, 1984

State of Connecticut
Department of Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council

Contact: Martha Johnson

December 12, 1985

POST MEETING COMMENTS RECEIVED

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National Capital Office
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Contact: Chuck Pace

Date: January 27, 1986

Chemical Manufacturers Association
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Washington, DC 20037

Contact: Ann M. Mason

Date: April 30, 1986

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee

Open Meeting

Under Public Law 92-463, notice is hereby given that a four-day meeting of the Halogenated Organics Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 14-17, 1986, in Conference Room 3906-3908 at Waterside Mall; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460. The meeting will start at 9:00 a.m. on January 14 and adjourn no later than 4:00 p.m. on January 17.

The purpose of the meeting will be to discuss draft drinking water Health Advisory documents for the following substances:

Carbon tetrachloride	Dioxin
Chlorobenzene	Epichlorohydrin
Dichlorobenzenes	Hexachlorobenzene
1,2-Dichloroethane	Polychlorinated biphenyls
1,2-Dichloroethylenes	Tetrachloroethylene
1,1-Dichloroethylene	1,1,1-Trichloroethane
Dichloromethane	Trichloroethylene
Dichloropropane	Vinyl chloride

The Halogenated Organics Subcommittee will not receive oral comments on the Health Advisory documents at the meeting. Written comments on any of the specific substances should be delivered within forty (40) days from the date of this notice to Manager, Health Advisory Program; Criteria and Standards Division [WH-550]; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460.

EPA's Office of Drinking Water prepared the draft Health Advisory documents. They are neither regulations nor regulatory support. To obtain copies of the draft Health Advisory documents for specific substances please write to the Manager of the Health Advisory Program at the above address.

The meeting will be open to the public. Any member of the public wishing to attend or to obtain further information should contact either Dr. Daniel Byrd, Executive Secretary to the Committee, or Mrs. Brenda Johnson, by telephone at (202)382-2552 or by mail to: Science Advisory Board (A-101F); 401 M Street, S.W.; Washington, DC; 20460, no later than c.o.b. on December 20, 1985.

Terry F. Yosie
Staff Director
Science Advisory Board

October 15, 1985
Date

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE
HALOGENATED ORGANICS SUBCOMMITTEE

Conference Room 3906-3908
Waterside Mall
401 M Street, SW
Washington, DC 20460
January 14-17, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

Opening Remarks	.....	Dr. Doull
Administrative Matters	.....	Dr. Byrd
Introduction	.....	Dr. Crisp Dr. Doull

*Tentative Sequence of Reviews, beginning Tuesday, January 14, 1986

Substance (Manager)		Reviewers
Carbon tetrachloride (Anderson)		Drs. Keller and Ahmed
Trichloroethylene (Khanna)	.....	Drs. Radike and Hornbrook
Dichloromethane (Khanna)		Drs. Keller and Hood
Dichloroethylenes (Crisp)	.....	Drs. Hornbrook and Lamm
Methylchloroform (Patel)		Drs. McMillan and Keller
Dichloropropane (Patel)	.....	Drs. Ahmed and McMillan
Polychlorobiphenyls (Khanna)		Drs. Hood and Safe
Tetrachloroethylene (Khanna)	.....	Drs. Radike and Safe
1,2-Dichloroethane (Khanna)		Drs. Ahmed and Abrahamson
Dioxin [TCCD] (Anderson)	.....	Drs. Safe and Hood
Vinyl chloride (Anderson)		Drs. Lamm and Radike
Chlorobenzene (Anderson)	.....	Drs. Rozman and Abrahamson
Epichlorohydrin (Anderson)		Drs. Abrahamson and Starr
Dichlorobenzenes (Anderson)	.....	Drs. Rozman and Starr
Hexachlorobenzene (Anderson)		Drs. Starr and Rozman

At the conclusion of the reviews

*Completion of reviews (previously deferred)	Dr. Doull
General comments	Dr. Doull
Nomination of Criteria Documents for further review	Dr. Doull

Other Subcommittee Business

Concluding remarks	.....	Dr. Doull Dr. Byrd

ADJOURNMENT

* The sequency in which the Subcommittee reviews Health Advisories for different substances and the time allocated to each review are at the discretion of the Chair.

United States
Environmental Protection
Agency

Office of the Administrator
Science Advisory Board (A-101)
401 M Street, SW
Washington, DC 20460

AB-EHC-87-006
October 1986

EPA

Review of Drinking Water Health Advisories by The Drinking Water Subcommittee of The Environmental Health Committee of The Science Advisory Board

- Acrylamide
- Benzene
- Dioxane
- Ethylbenzene
- Ethylene glycol
- n-Hexane
- Legionella
- Methyl ethyl ketone
- Styrene
- Toluene
- Xylenes (ortho-, meta- and para-xylene)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

September 20, 1986

SAB-EHC-87-006

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board [A-101]
U.S. Environmental Protection Agency
401 M Street, SW
Wasington, DC 20460

OFFICE OF THE ADMINISTRATOR

Dear Dr. Griesemer:

On January 6-8, 1986 the Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee publically reviewed eleven (11) draft health advisories for drinking water. Health advisories are described by the Office of Drinking Water as nonregulatory documents that are used to provide consistent, brief information to state and local health officials and personnel operating water works. During the review, the Subcommittee utilized Drinking Water Criteria Documents as support information for all of the health advisories except for p-dioxane, ethylene glycol, n-hexane and methyl ethyl hexane, for which the Subcommittee received copies of key papers from the scientific literature that support the calculations. The Subcommittee recommends that preparation of Criteria Documents for these four substances receive priority, because collections of key papers are not adequate support for the health advisories. Although the papers have the essential data, the bare facts are neither evaluated from EPA's perspective nor placed in logical context. EPA does not presently have source (or core) documents for these four substances.

The comments are divided into general advice, which is relevant to all of the advisories reviewed by the Drinking Water Subcommittee, followed by scientific advice specific to each of the substances reviewed. Because of the extensive nature of the comments, a Table of Contents and some supporting appendices are included. We appreciate the opportunity to become involved with this program and stand ready to provide further advice, as requested.

Sincerely,

Robert K. Tardiff

Robert Tardiff, Ph.D.
Chair, Drinking Water Subcommittee

Herschel Griffin

Herschel Griffin, M.D.
Vice-chair, Drinking Water Subcommittee

EPA NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency, and hence the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

TABLE OF CONTENTS

I. GENERAL COMMENTS OF THE DRINKING WATER SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA'S SCIENCE ADVISORY BOARD REGARDING DRINKING WATER HEALTH ADVISORIES

A. THE OFFICE OF DRINKING WATER (ODW) NEEDS TO CONSIDER HOW HEALTH ADVISORIES WILL BE USED.

Several groups of people will use health advisories, including state and local health officials (physicians, toxicologists, and engineers), water purveyors, and the general public. A physician will need clinical information, such as which biological tests are the most sensitive, both in terms of monitoring exposure and determining any potential health effects. Of particular importance are potential developmental or reproductive effects, increased sensitivity of a specific subpopulation, such as the young, and potential dermal effects which may occur from bathing. Water purveyors will desire concise statements of risk and "bottom line" numerical guidance for specific situations they may encounter. In most situations, they will have to meet the goal of the the lowest concentration, if the water is used for ingestion purposes. The general public will want information in easy to understand language and will want to know if it is "safe." The most useful format for the health advisory will provide at least the minimum, most basic information for all of these groups.

As currently written, the health advisories are aimed primarily at practicing toxicologists because of their fairly complete summaries of scientific data. However, additional information should be provided on dermal and inhalation exposures, since the ingestion route can easily be eliminated for a short time period by substitution of an alternative water supply. Guidance on showering and bathing is essential.

B. THE ONE AND TEN DAY ADVISORIES SHOULD BE RELATED TO EACH OTHER ACCORDING TO A SCIENTIFIC RATIONALE.

The one and ten day advisories are of of limited use for providing guidance for ingestion exposures. Public water supplies do not have milligram per liter concentrations of organic chemicals unless a spill has occurred. In those cases, the water source or the distributed water will not be used for drinking purposes for a short period of time. Moreover, if the contamination has just been found, no one will know how long people have been exposed to it, or how much time will elapse before the contamination is removed. Therefore, the long-term advisory will most often be used.

There are many examples in which the peak short-term concentration value of a substance produces maximal effects (not the total amount). This situation exists for some developmental effects, for example. On that basis, doubts exist about the adequacy of dividing a ten day advisory into its component parts.

For some substances, insufficient data exist to generate a ten day health advisory. There is no evidence in the literature of a repeated dose study having been performed for several days duration. The use of the one day health advisory as a starting point is in itself not wrong. Dividing by ten assumes that either the substance, or its effect, are strictly cumulative, which is the case for only a few substances. The health advisory level is intended to protect against injury, but cumulative injury is not expected.

A health advisory level based on the peak concentration of exposure would depend upon the half-life of the compound. If data are available, elimination rate needs to be considered. If the half-life is very short, the factor of ten may be excessive, especially in view of the safety factor already built into the one day health advisory. If the half-life of the chemical is long, or if accumulation is known to occur, the use of a factor of ten could be warranted. However, it would be peculiar to generate a ten day health advisory level lower than the longer term health advisory, adjusting for the fact that the ten day for health advisory is set for a child and the longer term health advisory for an adult.

C. THE ROUTINE ASSUMPTION THAT TWENTY PERCENT OF TOTAL HUMAN EXPOSURE DERIVES FROM DRINKING WATER IS UNWARRANTED.

An explanation is needed to address the default assumption that drinking water contributes a certain fraction of total exposure, where no data are available for a specific substance. The Subcommittee understands that the Office of Drinking Water often has to develop health advisories with inadequate (or absent) information. However, the current default assumption of a twenty percent contribution is particularly inappropriate for children and infants, on whom the one day and ten day advisories are based. The body surface area to body weight ratio is markedly different between infants and adults. Skin thickness (and dermal exposure) also may differ significantly between children and adults.

The automatic use of a twenty percent contribution from drinking water sources appears to be arbitrary. Further confusion results when the assumption of a twenty percent contribution is applied in some cases and not in others. The health advisories provide no explanations for these exceptions or for the default cases. For those cases where data are available regarding the possibility of exposure in the general public, a contribution calculated from these data should be used. The resulting contribution might be either higher or lower than twenty percent.

The Office of Drinking Water needs to consider inhalation and dermal exposures as additional confounding factors. These exposures could result from the use of water for purposes other than drinking, such as showering or cooking. Even for these factors, there are data for many of the compounds reviewed in this set of health advisories. These data include volatility and inhalational toxicity results. In a few cases dermal absorption rates also may be known. For many of these compounds the toxicity via the dermal route is known. In many cases these data are available from material safety data sheets. There may also be data available on the irritant properties of these substances.

D. THE ASSUMPTION OF A TEN KILOGRAM CHILD FOR EXTRAPOLATION TO INFANTS REQUIRES SOME MODIFICATION.

Just as children may respond very differently from adults, infants can be found to react very differently from children. This is particularly important when one considers that pediatric practice is able to sustain and

achieve survival of increasingly younger premature infants. In many instances, these children carry out in the incubator the kinds of developmental events that are more characteristic of in utero life, and they can be markedly more sensitive to exogenous agents than postnatal individuals. The way to solve these latter two problems is simply to add a general warning to alert the unwary reader that a health advisory based on adults or children might not be directly extrapolatable to increasingly younger and immature individuals.

E. BIODEGRADATION INFORMATION NEEDS A GREATER EMPHASIS.

The health advisories, in general, have a paucity of biodegradation information, which might be among the more valuable knowledge for officials of municipalities in dealing with specific contamination situations. Efforts to obtain such information from the literature should be carefully pursued in each instance, and no usable data should be ignored. In some cases, the Subcommittee does not know whether such information exists, or if the health advisory preparation process does not facilitate its aquisition.

F. OCCURRENCE AND TOXICITY DATA SHOULD BE CONSIDERED TOGETHER.

Most chemical substances are utilized in industry for a variety of purposes and are produced in varying amounts. A good example is the case of ethyl benzene, for which there is no Criteria Document and limited data for the health advisory. Ethyl benzene is manufactured in the amount of approximately 3.3 million tons per year. As a screen for deciding when to develop health advisories and/or Criteria Documents, ODW should make some attempt to correlate the occurrence and usage data of a compound with its potential as a hazardous substance. ODW can subsequently assign priority to those chemicals which have high usage or occurrence data. The Subcommittee understands that this is a complex matter. For example, in the case of a synthetic intermediate, there is little chance of public exposure from routine use, but substantial exposures can occur after accidental releases.

G. SOME PHYSIOLOGICAL ENDPOINTS MERIT INCLUSION.

In considering the adverse effects produced by a substance, it is important not to dismiss toxicological effects as simply being physiologic changes.† In the draft health advisories, certain changes were reported that appeared to be physiological responses or adaptations. For example, in the case of xylenes, ultra-structural changes were observed in the liver, but were considered as toxicologically insignificant. In other cases, increases in cytochrome P-450 were considered to be a toxicological endpoint. Toxicologists have debated the significance of such changes for years without developing a scientific consensus. In some cases, increases in the toxicity (activation) of a compound are observed and, in other cases, a decrease in the toxicity (detoxification) occurs. The problem with the current set of health advisories is a lack of consistency. Office of Drinking Water staff should decide how to carry out the evaluation of such physiological changes, and should use this policy consistently in the health advisories.

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† V.A. Newill, "Regulatory Decision-Making: The Scientist's Role," J. Wash. Acad. Sci., 64: 31-48, (1974).

H. PHARMACOKINETIC ANALYSIS IS IMPORTANT IN THE HEALTH ADVISORIES.

The Office of Drinking Water should attempt to provide pharmacokinetic data with the most recent references as well as the best references. Although the advisories generally compare animal data to human data and, in particular, where metabolites are thought to be responsible for toxicity, each advisory also should provide a careful assessment of the qualitative and quantitative differences. If different endpoints of toxicity exist in lower animals and humans, metabolic differences must be carefully considered. If the data base is sparse, this deficiency should be stated explicitly, at the beginning of the section in the health advisory.

I. THE ADVISORIES SHOULD NOTE ODOR THRESHOLDS.

Where odor and taste thresholds are lower than recommended levels, a note should be inserted in the health advisory to indicate that water potability or aesthetics may be an important consideration for field consideration, in addition to safety considerations. Each health advisory also should note where a particular substance present in the water is subject to sensory determination (odor, smell, color), or is determined analytically to be present and usually accompanied by other substances of equal or greater toxicity.

J. THE OFFICE OF DRINKING WATER SHOULD DEVELOP GUIDANCE, PERHAPS IN THE FORM OF AN ISSUE PAPER, ABOUT THE SELECTION OF DATA TO SET THE LEVEL OF AN ADVISORY.

Three subjects discussed by the Subcommittee relate to the concept of a hierarchy of data to be used in selecting studies for use in calculating advisory values. These include:

- Inconsistency in how no-observed-adverse-effect-levels were selected for different substances.
- Criteria to select pivotal studies.
- Use of information prepared by other organizations, such as the American Conference of Governmental Industrial Hygienists.

The Subcommittee recommends that a general and flexible hierarchy be formulated and followed consistently through the health advisory program. Specific points raised by the Subcommittee include:

- Advisories should be developed from data of appropriate exposure length and frequency. However, this should not lead one to calculate a "longer-term" or "lifetime" value substantially larger than a one day or ten day value.
- Oral exposure data should take preference over that from other routes, and drinking water studies are preferred over gavage studies. This is particularly true for gavage studies utilizing oil as a vehicle to attain large concentrations, and in particular where the vehicle alters absorption/pharmacokinetics.

- ODW states that the health advisories are based on the most-sensitive-observed-effects. It should characterize and state its views more clearly on the nature and significance of these effects. This decision will often be specific to the material for which the advisory is developed. For example, consideration of toxic effects from substances of similar structure or from studies of different duration may support selection of the "sensitive effect" as toxic.

- After it develops values for health advisories of different durations for a substance, the Office of Drinking Water should review the entire data base to determine the consistency of individual calculations with each other. A prior description of the underlying logic for which such decisions are made will be useful guidance for preparing advisories.

- For some materials, (e.g. benzene, hexane) there are human toxicity and/or exposure data by other than oral routes. These data may be considerable, involving a good estimate of body burden, and may provide additional data for a no-observed-adverse-effect-level or lowest-observed-adverse-effect-level evaluation. The Environmental Health Committee and its Subcommittees have consistently urged the Agency to take advantage of these kinds of "experience checks."

- The American Conference of Governmental Industrial Hygienists has been active for many years in the setting of Threshold Limit Values. Threshold Limit Value is a registered trade mark of American Conference of Governmental Industrial Hygienists (ACGIH). ACGIH frequently reevaluates these values and publishes the scientific basis of each one. They may be considered concensus values based on the best available published data. While there is some hesitancy to use the Threshold Limit Values because the route of exposure is frequently by inhalation, they often are based on human data. It would be interesting to determine how many of the health advisories cite the same references as those given for the Threshold Limit Values. The Office of Drinking Water might initiate a health advisory with this set of references for purposes of efficiency. The Threshold Limit Value documentation also frequently contains other useful pieces of information. For example, they may cite the lowest doses associated with mortality or other signs or symptoms of toxicity. In addition, they may contain information on irritancy and odor threshold.

- Where the Office of Drinking Water hesitates to use the human inhalation data from a Threshold Limit Value or chooses to use animal oral data, it might be useful to compare the two values. However, the Subcommittee is of a divided opinion regarding the desirability of such calculations. A value based on human inhalation data could be calculated by extrapolating from inhalation to oral route. The difference in safety factors for animals versus humans would also have to be considered, and Threshold Limit Values are established for eight hours per day exposure of healthy workers. Threshold Limit Values should be used only for non-route specific target organ effects. For example, it is not appropriate to set a drinking water value for a metal which causes fume fever when inhaled. Beyond this specific caveats, some members of the Subcommittee urge caution in extrapolating from human occupational inhalation standards to environmental standards for the general population

since the workplace standards often are developed from experience at existing occupational exposures. Thus, the Theshold Limit Values often have an empirical, tentative status and are subject to downward revision as more experience accumulates. In such a situation, comparison to an environmental standard mean to provide safety for the general population can be misleading.

K. THE PRESENCE OF CERTAIN COMPOUNDS IN DRINKING WATER CAN INDICATE THE PRESENCE OF OTHER SUBSTANCES FROM A COMMONLY OCCURRING MIXTURE.

Some of the compounds for which health advisories exist are most likely to be found as part of a mixture. Hexane will probably be found as a component of gasoline, and other components, such as benzene, toluene, xylenes, and ethyl benzene, also may be present. In this case, hexane serves as an indicator or sentinel substance. The health advisory for each of the components should mention this possibility and present some guidance as to how the presence of the total mixture should be evaluated. For example, in the health advisory for toluene, a note might be added that when toluene is found, the reader should also examine the monitoring data for the possible presence of other compounds found in gasoline. If found, the reader should review the health advisories for gasoline related substances, such as benzene, followed by a listing of the gasoline related substances for which advisories exist. The Office of Drinking Water should consider the devlopment of a health advisory for gasoline.

L. THE EXPOSURE ANALYSES THAT SUPPORT HEALTH ADVISORY CALCULATIONS MERIT SOME MODIFICATION.

The health advisories only consider ingestion of two liters of water as the route of exposure. Drinking water contamination can also lead to inhalation and dermal exposure. The advisories should consider these two routes of exposure especially when they address high contaminant levels.

Exposure to contaminants in drinking water occurs not only through the two liters of water that ODW assumes a person drinks in one day. Exposure from drinking water also occurs through dermal absorption and through inhalation of volatile compounds. Because the average per capita use of domestic water approximates 120 liters, which is more than the two liters estimated in the health advisory for oral consumption, these other exposure routes are potentially significant on a mass balance basis. Moreover, if drinking water is obtained from contaminated ground water, the indoor air quality in homes above the ground water can be affected.

Human exposure to some of the compounds considered in the health advisories occurs not only through water but through the air, food, soil and dust. When deriving health advisory values, these other routes of exposure must be considered, and the entire Acceptable Daily Intake can not be allocated to drinking water. In most cases, exposure information will not be complete. Even though an estimate of the known exposure may be possible, ODW should make allowances to ensure that the Acceptable Daily Intake is not exceeded. Therefore, the health advisory should include information on whether or not the compound is absorbed through the skin and whether or not it is a skin irritant.

Users need the one and ten day health advisories to make decisions and provide information on whether or not the water is suitable for bathing and showering purposes since the ingestion route can be avoided for limited time periods by issuing a bottled water order. EPA should consider providing some advice on not using a contaminated raw water source when possible, especially if the contamination is the result of a spill and the source is not essential.

If substantial differences exist in the health effects of a substance when exposure occurs through inhalation rather than ingestion, the health advisory should indicate this difference. If the compound contributes to indoor air pollution, this information should be stated explicitly.

If a health advisory number derives from an acute or subacute effect, EPA should consider basing the number only on a child or infant, not an adult. If a study of chronic effects (lifetime study) drives the value of a health advisory, EPA should develop only the value for an adult.

M. ODW SHOULD IMPROVE THE EDITORIAL QUALITY AND CONSISTENCY OF THE DRAFT HEALTH ADVISORIES.

Overall, the Subcommittee found a high level of proofreading and citation errors. The health advisories did not describe the properties of the substances in a consistent manner, and factual matters, such as molecular weights, were misquoted with a high frequency. In addition, the Subcommittee has pointed out many errors in the calculations. The Subcommittee has not provided a comprehensive technical editing for the health advisories. Therefore, it recommends that the Office of Drinking Water provide for a thorough technical editing before it releases the final versions.

The Office of Drinking Water provided constructive comments on the use of health advisories by states and localities. Both the Subcommittee and EPA have concerns about potential misuse of the health advisories. For example, if the terminology regarding developmental effects is not articulated clearly, the health advisories will be counter-productive of embryonic well-being by tending to generate unwarranted elective abortions. The label "teratogen" refers more often to the dose at which exposure occurred in an animal study than to some intrinsic property of the chemical itself. The current practice tends not to emphasize selective effects on the conceptus. The Subcommittee recommends that the Office of Drinking Water use the terminology of "developmental toxicity" instead of "teratology." Teratology is but one of the four signs of developmental effects.

II. COMMENTS OF THE DRINKING WATER SUBCOMMITTEE ON HEALTH ADVISORIES FOR SPECIFIC SUBSTANCES

A. ACRYLAMIDE HEALTH ADVISORY

The Criteria Document is dated October, 1985, but it fails to include some relevant recent data, including key papers published in 1983. The health advisory, which closely reflects the contents of the Criteria Document, also lacks these references. They may not be important for calculating safe exposure levels but, because they relate to some of the more subtle effects and mechanisms of toxicity, they possess implications for the assessment of long-term adverse effects. To update the references, the Subcommittee recommends the use of some standard computerized literature retrieval service. The Subcommittee provided a printout to Office of Drinking Water staff as an example. The health advisory also has a large number of editorial and typographical errors. For example, the chemical structure of acrylamide is in error.

The Criteria Document for Acrylamide is not an integrative, critical review, but largely consists of a series of descriptions of individual studies. For this reason, it misses a significant aspect of the acrylamide literature: the consistent reports that, first, sensory systems are damaged before motor systems and, second, that detection of functional impairment (behavioral, electrophysiological, neurochemical) often precedes histological damage.

Both the Criteria Document and the health advisory do not adequately discuss the question of dose-duration relationships. They assert that evidence of acrylamide neuropathology is manifest after a cumulative dose of 100-150 mg/kg, but this conclusion is warranted only within a narrow range of dose rates. In some experiments, a single dose of 50 mg/kg to rats inhibited nerve terminal sprouting. This work was not reviewed in the health advisory. In contrast, a dose rate of 1 mg/kg·day induced clinical signs of neurotoxicity in monkeys only after 18 months of treatment and a presumed cumulative dose of about 400 mg/kg. Enough data are available in the literature to calculate a relationship between dose rate and toxicity.

The time dependency of acrylamide dose is deceptive. The pharmacokinetic half-life is between 2 to 5 hours, but metabolites last longer, and the toxic behavioral effects are inconsistent with the pharmacokinetics. One to two weeks after a 10 mg/kg dose in the cat, symptoms appear. At 1 mg/kg·day, symptoms appear after 18 months. Extrapolation based on pharmacokinetic analysis is unwarranted. The exposure calculations would be modified slightly by basing them on 1982 data indicating behavioral effects after a single dose of 10 mg/kg to rats. Collateral neurochemical data also yield the same dose level as at least a lowest-observed-adverse--effect-level. The description of absorption should reflect that acrylamide can be absorbed through unbroken skin as well as through mucous membranes and lungs.

The section on synonyms is incomplete. The Subcommittee recommends that the Office of Drinking Water use a standard source, and it has provided the

program with a printout from a standard commercial source. The section on uses also is incomplete. The health advisory could add data on solubilities in chloroform and benzene, since there is no available octanol/water partition coefficient.

In the short-term exposure section, the analysis should reflect that McCollister used female rats, male guinea pigs and rabbits of both sexes. Pryor reported an acute LD_{50} of 203 mg/kg and subchronic values of (5 days/week/4weeks) LD_{50} of 32 mg/kg and subchronic (5 days/week/15weeks) LD_{50} of 17 mg/kg. In the longer-term exposure section, the advisory should provide a reference for the value cited in the first section, and move the second, fourth and sixth sections to the section on short-term exposure to reflect the dosing. McCollister reported additional no-observed-adverse-effect-level data for rats, cats and monkeys that are not reflected in the health advisory. The drinking water equivalent level calculation should be based on 0.0002 mg/kg·day instead of 0.002 mg/kg·day. There is an error in the calculation. The EPA standard given in the Criteria Document is 0.05%, not 0.05 ug/L.

B. BENZENE HEALTH ADVISORY

The benzene health advisory effectively organizes data from diverse sources and places them into perspective. However, the status of the Criteria Document is not clear, and it differs in places with the health advisory. The Criteria Document appears to be a preliminary draft because of the inconsistent styles between each section and because the logic wanders. The two documents also are inconsistent. For example, the Criteria Document does not mention ground water in extent or significance, but the health advisory states that benzene is released to the ground, binds somewhat to the soil, slowly migrates to ground water and remains stable there.

Several synonyms often are confused with benzene, such as benzin or benzol, and they merit inclusion. Where information exists on mixtures containing benzene, the health advisory should use it. For example, the Criteria Document mentions that the simultaneous treatment with both benzene and toluene or piperonyl butoxide increases the excretion of benzene in breath. The odor threshold for benzene is of considerable importance. No mention is made of the metabolites of benzene, which include phenol, catechol and hydroxyquinone.

The preponderant scientific evidence suggests that benzene is metabolized through formation of an epoxide, which contrasts with the inconclusive statement in the health advisory that different metabolic pathways are involved. For risk assessment, it is important to note that 47% of benzene inhaled was absorbed, 30% retained and 16% exhaled unchanged, when exposed to 52-62 ppm for 4 hours, and was the same for both sexes. Benzene absorbed from ingested drinking water or inhaled from drinking water sources will be subject to these pathways. More detailed information on dermal absorption is needed. The Criteria Document also mentions three elimination phases for humans versus the biphasic results described elsewhere. This descrepancy should be resolved.

Neither the study by Dosken nor that by Chang states that the lowest level of benzene to produce platelet effects in workers was 10 ppm, which represents a modelled result. The description of short-term health studies by Wolfe and coworkers should include a description of duration of exposure.

The description of the Occupational Safety and Health Administration standard as 3.2 microgram/L is in error. The standard is 32 milligrams/M^3.

C. DIOXANE HEALTH ADVISORY

The health advisory for 1,4-dioxane constitutes a useful document, but some errors merit correction. The range of dioxane concentrations found in drinking water needs to include a perspective on these data based on the hazard information in the health advisory. The Subcommittee suggests that the health advisory point out that 1,4-dioxane is a synthetic organic compound with no known natural sources. Dioxane is mixable with water at all concentrations, and it may be that its mobility in soil is directly proportional to water passage through the soil.

Given the importance of biodegradation and/or spontaneous degradation information, the Subcommittee recommends a further search of the literature. The current review appears out of date. Degradation by chlorination, which will occur in many drinking water supplies, results in products which are more toxic than the parent compound. The fact that the test material may become chlorinated and thereby become markedly more toxic than the parent compound is not a valid basis for not determining a health advisory. The fact of potential chlorination, with or without altered molar toxicity, is relevant, however, to other aspects of an health advisory, i.e., other criteria, guidance and standards. Since this detail is reported in the longer-term health advisory section, many operating personnel may miss it.

The health advisory for dioxane assumes one hundred percent absorption from the gut. The Subcommittee recommends the addition of a discussion about the cutaneous and pulmonary routes as well.

Covalent binding of 1,4-dioxane was higher in the nuclear fraction than in other cell fractions. The Subcommittee suggests adding a perspective on the extent or absence of covalent binding with DNA and its implications.

Metabolism of dioxane is dose-dependent and saturable. The relevant data are cited but not interpreted. The first sentence of the excretion section speaks of "animals," but if reports from species other than the rat exist, they should be reported. The rate, as well as the form of excretion, constitutes important information.

The health advisory cites the 1979 National Institute of Occupational Safety and Health Registry to provide the oral LD_{50} values in several species. Some of the references of the Registry also report effects at lower doses and, if these were reported, one would have information significantly more useful than isolated LD_{50} values. The discussion of acute pathology is very limited, and there may be additional published target organ toxicity information available. The description of the work of Fairley and coworkers with rabbits is difficult to understand. It merits not only rewriting but also expansion. Overall, the slopes of dose-reponse curves should be given, where possible.

The nature of the tumors reported in the study of Kociba and coworkers merits discussion.

Several studies in chickens may be useful in evaluating the developmental aspects of 1,4-dioxane. A mouse study of some utility existst. There are numerous examples of solvents that represent significant hazards to reproduction. Structure activity relationships for reproductive (but not developmental) effects also are possible in some limited instances, such as alkylating agents and some classes of hormones. This information merits a renewed literature search for relevant data.

Several reports of in vitro mutagenicity tests of 1,4-dioxane occur in the literature that are not cited in the health advisory, and the Subcommittee recommends further searching for similar studies.

The relevance of the calculation of no-observed-adverse-effect levels for a substance with carcinogenic potential, such as dioxane, merits discussion in addition to the retrospective predictive ability of the formula presented. The use of body weight is an essential component of such calculations, but they fail to account for the marked differences among individuals based on age alone. The consumers who take in the largest relative volume of liquid are infants. Awareness of this factor could be one of the qualifiers applied to this calculation. The dangers of extending the mg/kg calculation to the newborn or prematurely delivered infant merits mention. How was the safety factor of 100 for "animal data" arrived at? Retrospectively, how proper has it proven?

With respect to the one day advisory, it is difficult to consider how intravenous dose groups of one animal, each with effects seen in the animal treated at the lowest dose, leads to a useful lowest-observed-adverse-effect-level without carefully reviewing supporting data. However, such an extended rationale is not available in the health advisory. The extrapolation needs a discussion (or citation for a supporting explanation) of its range of limitations. The Subcommittee prefers the use of an acute oral toxicity study to an intravenous study, given the scant knowledge of pharmacokinetics of dioxane.

The fact that an acceptable study for calculating a ten-day health advisory was not located does not justify dividing the one-day health advisory by ten. There are instances where it is not the area under the curve that is proportional to response, but instead the peak level attained that exceeds a threshold of response.

The absence of acceptable data to set a short-term standard and the possibility of enhanced toxicity after biodegradation do not constitute valid reasons to set aside the development of a longer-term health advisory. In other advisories, the Office of Drinking Water has developed longer term health advisories for substances with carcinogenic potential, and some consistency is needed. The data of Kociba and coworkers will support the development of both longer term and lifetime health advisories.

The Subcommittee suggests further literature searches on the topics of movement in ground water and other water degradation, biologic half-time and perhaps bioaccumulation potential.

A degree of value judgment and/or guidance is merited in the analysis section. The paragraph offered is not meaningful in guiding the reader to the appropriate technique.

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† See Toxicology letters 12: 191-198 (1982).

D. ETHYLBENZENE HEALTH ADVISORY

With the exceptions noted below, the health advisory is consistent with information presented in the Drinking Water Criteria Document for Ethylbenzene. Overall, acceptable daily intake calculations are consistent with guidance provided in the issue papers for such calculations.

The health advisory should include "tobacco smoke constituent" as a source of exposure to ethylbenzene since this source results in the highest exposure amounts in ambient air. Similarly, motor vehicle exhaust may reasonably be expected to result in exposure.

The pharmacokinetics section needs modification. The Criteria Document should include several important references† published in 1984 that provide new information on the metabolism and excretion of ethylbenzene in rats.

The uncertainty in human health effects reported at 100 ppm is not properly presented. The report of Bardodej and Bardodejova states that the total number of volunteers was 18. The authors report that exposure to 100 ppm caused no ill effects. Duration of exposure was not specified in the Criteria Document, but an increase in exposure resulted in reported symptoms of sleepiness, fatigue, headache and mild eye and respiratory irritation. The authors did not report the increase in exposure that caused these symptoms.

This report does not attain the same quality as information considered in establishing and maintaining the present American Conference of Governmental Industrial Hygienists Threshold Limit Value of 100 ppm. Most available information indicates that 100 ppm-8 hour exposure represents a no-adverse-effect-level, not an effect level.

The mutagenicity section needs improvement because the health advisory fails to cite the work of Dean and coworkers* which reports that ethylbenzene is not mutagenic in Salmonella typhimurium, E.coli, S. cervisiae and in the recessive lethal chromosome assay in Drosophila.

The National Cancer Institute has not yet initiated a bioassay for carcinogenicity of ethylbenzene. Activity is at the design committee stage.

No rationale exists to support the establishment of a ten day health advisory value through the procedure of dividing the one day value by ten, when ethyl benzene (1) appears to have a threshold, and (2) seems to be rapidly metabolized and cleared from the body. A consortium of ethylbenzene producers is currently conducting 28-day inhalation probe studies in mice, rats and rabbits. These studies should provide better data for calculating short-term health advisories.

No data are presented to support the conclusions about treatment of water.

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† K. Engstrom, "Urinalysis of Minor Metabolites of Ethylbenzene and m-Xylene," Scan. J. Work. Env. Health 10: 75-81 (1984); K. Engstrom, "The Metabolism of Inhaled Ethylbenzene in Rats," Scan. J. Work. Env. Health 10: 83-87 (1984); K. Engstrom and Coworders, Int. Arch. Occup. Env. Health 54: 355-363 (1984).

* B.J. Dean and Coworkers, "Genetic Toxicology Testing of 41 Industrial Chemicals," Mutation Research 153: 57-77 (1985).

E. ETHYLENE GLYCOL HEALTH ADVISORY

No Drinking Water Criteria Document is available for ethylene glycol. The health advisory derives from a number of key references and, in general, adequately reflects the contents of the journal articles cited. The studies by Mason are correctly transcribed, but it is not clear how thoroughly the pathology portion of the study was conducted, other than the tumor counts. For example, what is meant by selected tissues? How carefully were the kidneys examined?

The only study reported under the section of developmental and reproductive effects is that of Elis and Raskova. However, their report lacks experimental detail.

The study by Blood and coworkers represents a key reference and is used in the calculation of the longer-term health advisory. This study used only three monkeys, and the experimental details in the report are sketchy. Another study which EPA should consider is that of Roberts and Seibold which also studied monkeys at various doses although for shorter periods of time.[1] This study found kidney damage in the absence of calcium oxalate crystals which required a dose of 15 ml/kg or greater for formation.

The study of Laug and coworkers adequately describes the acute effects in a variety of animals, but the study by Reif is questionable. It does not constitute a well controlled study but merely reported observations on one individual. More information on humans is available, including a number of studies in the literature on the toxicity of ethylene glycol. These studies are addressed in reviews and texts.[2] Also, studies of individual cases have demonstrated a wide range of sensitivity among humans to the toxic effects of ethylene glycol. The paper by Reif may not be adequate to estimate percentages of metabolites. Ethylene glycol elimination is a very dose dependent process which has been documented well in animal studies, such as those by Marshall.[3] Dose dependency of elimination works strongly against the use of high doses to make estimates on long term, low level exposures.

EPA should review a number of other multiple dose studies in animals, such as that of Rajagopal and Ramakrishnan,[4] which also list other

[1] J.A. Roberts and H.R. Seibold, "Ethylene Glycol Toxicity in the Monkey," Toxicology and Applied Pharmacology, 15: 624-631 (1969).

[2] See, for example, Haddan and Winchester, Clinical Management of Poisoning and Drug Overdose; R.W. Moriarty and R.H. McDonald, "The Spectrum of Ethylene Glycol Poisoning. Clinical Toxicology," 7: 583-596 (1974); C.D. Peterson and Coworkers, "Ethylene Glycol Poisoning: Pharmacokinetics during Therapy with Ethanol and Hemodialysis," New England Journal of Medicine 304: 21-23 (1981).

[3] T.C. Marshall, "Dose-dependent Disposition of Ethylene Glycol in the Rat After Intravenous Administration," Journal of Toxicology and Environmental Health 10: 397-409 (1982).

[4] G. Rajagopal and S. Ramakrishnan, "Effect of Ethylene Glycol Toxicity on Hepatic Carbohydrate Metabolism in Rats," Toxicology and Applied Pharmacology 46: 507-515 (1978).

relevant references. The study by Gessner and coworkers on metabolism and the study of Marshall also are germane.

Another important factor is the literature base used to develop the Threshold Limit Value by the American Conference of Governmental Industrial Hygienists. Although many of the data relate to studies conducted by using the inhalation route, there are a number of good studies referenced.

In summary, the Health Advisory on ethylene glycol represents a reasonable distillation of the references used. However, it suffers from the omission of useful data generated in the last decade and underestimates what is already known about the toxicity of this compound in humans. In addition, recent incidents will generate new data on human exposure by ingestion.

F. n-HEXANE HEALTH ADVISORY

Since no Drinking Water Criteria Document for n-hexane exists, the health advisory is based on a collection of supporting papers. The health advisory omits recent references dealing with metabolism and toxicity, especially with the agents responsible for toxicity. It also lacks some papers dealing with toxicity and mechanisms.

The 1290 mg/kg dose used as the basis of most calculations is difficult to justify. With a substance producing an irreversible toxicity it is necessary to understand the mechanism, the metabolite responsible and the rate at which humans might be expected to produce the metabolite. If this kind of explanation cannot be provided for n-hexane, EPA should explore this issue and provide a rationale for the method though which it calculates the safety levels.

In the study by Heshkowitz and coworkers, the exposures averaged 650 ppm with peaks up to 1,300 ppm, instead of ranging between these two levels. In the study by Krasavage and coworkers, it is not clear that the 1,140 mg/kg dose was administered for 120 days. The paper could be interpreted as indicating that the 1,140 mg/kg dose was given for 90 days. ODW should re-evaluate if the dose of n-hexane in the study by DiVincenzo and coworkers may be 250 mg/kg and not 450 mg/kg.

Nerve conduction velocities may be one of the more sensitive indicators of impairment by n-hexane. The experiments used to calculate the health advisories were not based on these endpoints, nor was this mentioned in the health advisory.

The health advisory mentions furan and valerolactone derivatives as metabolites of n-hexane. In discussing metabolites of methyl n-butyl ketone, DiVincenzo and coworkers indicate that a furan derivative may be formed in the gas chromatograph and may not actually be a metabolite of methyl n-butyl ketone. The same artifact may occur with n-hexane and its cyclic derivatives. The level of 2-hexanol referred to in the excretion section section should be 0.5 mg/liter and not 0.05 mg/liter. The hexane used was commercial hexane and not pure n-hexane. The study by Bus and coworkers shows that n-hexane and its metabolites reach the fetus. The reproductive section should state this conclusion.

The Subcommittee suggests that, given the amount of information available about human industrial exposures and abuse, the advisory could base the calculations directly on the human data. The drinking water issue paper by Khanna, which discusses the conversion of inhalation data into drinking water standards, provides one means of doing so. Also, it would be useful to apply such a technique to the Threshold Limit Value. At a minimum, a calculation based on human data can compare with the current calculation as an "experience check." Information on respiratory uptake and retention of hexane also would be useful, if EPA extrapolates between the oral and inhalation route. Inhalation experiments indicate that continual exposure may be more toxic than intermittent exposure. In addition, Perbellini and coworkers suggest that humans may be more susceptible to n-hexane than experimental animals based on the different

ratios of metabolites among the species. The advisory should address these possibilities as part of the experience check.

EPA should incorporate into the health advisory the issue of the toxicity of mixtures of which n-hexane is a constituent. The paper referred to in the health advisory reports that the hepatotoxicity of chloroform is greatly enhanced when simultaneous exposure to n-hexane occurs. Water supplies are unlikely to be contaminated with only n-hexane, and the health advisory indicates that the major source of hexane in the environment will be gasoline. However, the health advisory does not mention how this should be factored into the use of the values given.

Since other gasoline components will accompany n-hexane contamination most of the time, additional guidance on how the health advisories should be altered for the complex mixture would prove valuable. It may be worthwhile to note that some gasoline components have been associated with carcinogenic effects and that gasoline itself is probably is carcinogenic for humans. Office of Drinking Water staff should consider whether it may be a better strategy to issue a health advisory for gasoline, rather than deal with possible problems in a piecemeal fashion.

For a volatile substance like n-hexane, the greatest need for the one- and ten-day advisories will be to provide guidance as to whether or not the water can be used for bathing and to provide information on the adverse impact on indoor air quality. The exposure scenarios only use ingestion as the route of exposure, which can easily be eliminated by issuing an advisory against the use of the contaminated water source for drinking and cooking purposes, or in the case of the one-day advisory, not using the contaminated raw water source and using stored water. Information on whether or not hexane is absorbed dermally would provide some indication of the potential for exposure while bathing.

The Subcommittee suggests some additional references as a basis to initiate revision of the health advisory:

Baker and Rickert, "Dose-dependent uptake, distribution and elimination of inhaled n-hexane in the Fischer-344 rat," Toxicology and Applied Pharmacology, 61: 414-422 (1981).

T.A. Marks, et al, "Influence of n-hexane on embryo and fetal development in mice," Drug and Chemical Toxicology 3: 393-406 (1980).

Raje, "In vitro toxicity of n-hexane and 2,5-hexanedione using isolated perfused rabbit heart," J. Tox. and Env. Health 11: 879-884 (1983).

Lungarella et al, "Respiratory tract lesions induced in rabbits by short-term exposure to n-hexane," Res. Comm. in Chem. Path. and Pharm. 29: 129-139 (1980).

Kronevi et al., "Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs," Env. Res. 19: 56-69 (1979).

Jakobson et al., "Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs," Tox. and App. Pharm. 63: 181-187 (1982).

Howd et al, "Relation between schedules of exposure to hexane and plasma levels of 2,5-hexanedione," Neurobehavioral Tox. and Teratology, 4: 87-91 (1982).

Couri and Milks, "Toxicity and metabolism of the neurotoxic hexacarbons n-hexane, 2-hexanone, and 2,5-hexanedione," Ann. Rev. Pharmacol. Toxicol. 22: 145-166 (1982).

Calvender et al, "A 13-week vapor inhalation study of n-hexane in rate with emphasis on neurotoxic effects," Fund. and App. Tox. 4: 191-201 (1984).

Bravaccio and Ammendola, "H-reflex behavior in glue (n-hexane) neuropathy." Clinical Tox. 18: 1369-1375 (1981).

Graham et al, Tox. Appl. Pharm. 64: 415-422 (1982).

G. LEGIONELLA HEALTH ADVISORY

The Subcommittee questions the classification of potential bacterial pathogens in water as toxic substances on the basis that bacterial cells are complex, dynamic entities, capable of replication. Placing them into the same group as toxic substances may not be appropriate.

The format of the health advisory for Legionella differs from that of the chemical substances, perhaps in recognition of the incongruence. However, EPA should articulate the rationale for the difference, and the Subcommittee recommends that the emphasis of the final health advisory be placed on surveillance of respiratory illness, not drinking water.

Twenty-three recognized species of Legionella exist, twelve of which have been implicated by culture techniques as sources of pneumonia. One species, L. pneumophila, causes approximately 85% of these cases. With only one exception (L. feeleii), L. pneumophila has been implicated as an agent for Pontiac Fever, although no isolates of legionellae have been obtained from patients with Pontiac Fever. Thus, grouping all legionellae as pathogens with equivalent virulence cannot be justified at this time.

Most public health officials would agree that an advisory on legionellae is needed at this time, because of numerous inquiries by the public, especially engineering personnel and health officials given the responsibility of taking appropriate measures to prevent the spread of Legionella from water in their facility. However, the advisory should emphasize that epidemics and sporadic cases should be dealt with on a case-by-case basis. The beginning of the advisory should state the following: (1) The source for the spread of legionellosis or Pontiac Fever should be determined epidemiologically before intervention. It does not make sense to attempt widespread eradication of mostly nonpathogenic organisms, when the pathogenic strain can be traced. (2) Environmental strains implicated as a cause of disease should be matched with patient isolates. (3) Routine monitoring of water for Legionella is not recommended. (4) There is no all encompassing disinfection procedure that can be recommended each time.

Although the health advisory is not legally enforceable, the Subcommittee understands that it will be accepted by some workers as policy for installation and maintenance of plumbing systems. The guidance in the health advisory focuses on how to deal with a problem once it is recognized, rather than how to decide when one has a problem. The Subcommittee recommends the following sequence of investigation as more appropriate:

- Given the impossible task of eradicating legionella, legionellosis appears selective for high risk individuals. The attention of clinical and public health workers should focus initially on surveillance for respiratory illness, especially in high risk patients. If an increase is detected, they should attempt to establish the etiology, not by culturing the water but by culturing the patients and by performing serologic studies. Microbiological analysis of clinical specimens is as rapid as culture of environmental specimens, and preliminary information can be gleaned from acute-phase serological specimens.

• If Legionella is implicated in an outbreak of clinical illness, public health officials should attempt to culture environmental sources. They may undertake temporary measures designed to control environmental legionellae, while using modern molecular techniques to determine if the source has, in fact, been identified correctly. If all the data suggest a clinical problem, and that it is probably associated with a particular environmental source, continuing effort should be directed at that source because past experience suggests that the problem may recur.

• Maintenance of decontamination procedures should occur in a way to minimize danger to individuals and damage to the plumbing systems. A careful program of microbiologic monitoring of the environment and clinical monitoring of human disease represents an integral part of that program because it cannot be assumed that the problem has been controlled indefinitely. A focus on a few problem sites makes much more sense than a dilution of effort by attacking all potable water systems. When dilution of effort occurs, the likely result is that none of the sites is treated optimally.

• The Subcommittee also has several technical corrections to improve the accuracy of the final health advisory, as follows:

• The importance of matching the patient isolate with the environmental isolate from a source implicated by epidemiologic data should be discussed in more detail. Also, grouping and characterization of L. pneumophila strains by isoenzyme profiles may be more definitive than monoclonal subgrouping.†

• The contamination of a water system by new distribution components is not well documented.

• Since legionellae can reside in cold water pipes, disinfection of a plumbing system by heat treatment alone is not as effective as the combination of heat treatment and chlorination. Chlorination without heat treatment has been effective in several cases. Growth of legionellae may theoretically be enhanced on the cold water side of a hot-cold water mixing valve in a heat-treated plumbing system.

• Since the overall cost of using heat for disinfection is greater when considering all of the costs such as personnel time to monitor heat treatment, cost of the heating, costs for precautionary measures taken against scalding, and the cost of periodic treatments, this factor should be discussed when comparing the advantages and disadvantages of chlorination versus heating.

• The health advisory should state that ozone, ultraviolet, and ethylene oxide methods for disinfection of legionellae have not proven effective in field tests. The advisory should note the difficulties of controlling manual batch chlorination and the availability of devices that continually monitor and adjust chlorine levels.

• Information on the specific types of gaskets and fittings that support the colonization of legionellae is not well documented. More research is needed to confirm published reports, and make recommendations on acceptable materials.

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† R.K.Selander and Coworkers, "Genetic Structure of Populations of Legionella pneumophilia," J. Bacteriol. 163: 1021-1037 (1985).

H. METHYL ETHYL KETONE HEALTH ADVISORY

The Office of Drinking Water has not prepared a Criteria Document for methyl ethyl ketone. Instead, it included key references for calculating the health advisory values. Although the data base for methyl ethyl ketone is meager, it appears adequate for the purpose of calculating these values. The evaluation of the literature is reasonable, and the values correct, except that the lack of a ten day advisory is inconsistent with the use of subchronic data.

Similar to the situation with n-hexane, the mixtures problem needs to be addressed especially since methyl ethyl ketone enchances the neurotoxicity of n-hexane. That combination is suspected as responsible for the outbreak of neuropathies among substance abusers in West Berlin who, until the addition of methyl ethyl ketone, seemed to suffer relatively mild toxicity.

Although the advisory makes statements concerning the dermal absorption and the quantative nature of certain metabolites, the Subcommittee is not aware of adequate studies dealing with distribution and metabolism. The lack of adequate studies merits greater emphasis and should preceed the paragraphs on absorption and metabolism.

I. STYRENE HEALTH ADVISORY

The health advisory has addressed the major scientific issues in the Criteria Document on Styrene. Except as noted below and in the general comments sections, it has appropriately summarized and drawn sound conclusions.

The styrene health advisory notes that experiments in humans support the use of no-observed-effect-levels based on central nervous system effects. The one-day exposure level, however, derives from a study that relied on hepatotoxic endpoints. It also seems inconsistent that the longer term acceptable daily intake is equivalent to the 10-day health advisory for a child and quite close to the one-day health advisory. The health advisory should offer some explicit cautions.

In the section on distribution, the radioactivity detected was styrene or its metabolites. The health advisory should also specify where in the molecule the ^{14}C label was located.

In the section on transplacental transfer, the measurement of transferrred styrene was made on cord blood. This does not imply a one-way transfer but rather a selective concentration on the fetal side of the placenta. This could be the result of an equilibrium in a two-way transfer situation.

ODW should expand the section on metabolism to include a more extensive treatment of styrene oxide, which is is a highly reactive chemical, a carcinogen and a mutagen. It would be valuable to know what percentage of styrene gets metabolized to styrene oxide and how this might vary from organ to organ. The effect of dose on metabolism should also be described. Many studies on mercapturic acid formation have not been included.

In the developmental and reproductive effects section, the advisory should comment that the doses studied were 300 mg/kg·day or less, and that these were comparatively low doses. Effects are possible at higher doses. Perhaps it would suffice to add a parenthetical statement at the end of the paragraph noting comments on the comparatively low doses. The dose of styrene oxide should be specified and noted as a source of concern. In the Finnish study the control incidence was 8% and the exposed 15%. The control incidence is the unusual finding, since in many comparable studies, it is 15%.

Considerably more evidence about the mutagenicity of styrene oxide exists than is described in the health advisory. It would be valuable to add information about mutagenicity in other systems including mammmalian cells. Activity as measured with a number of other endpoints, which are not necessarily mutagenic but related, might also be noted, such as sister chromatid exchanges, chromosomal abnormalities, and so forth.

The data regarding the carcinogenicity of styrene is complicated and deserves somewhat more discussion in this section. The statement about excessive mortality suggests that the study by Ponomarkov and Tomatis was done poorly. Instead, there were many early deaths related to treatment

in this study, and among the animals dying early there were an excess of lung tumors including a disproportionate share of malignant tumors. More discussion of these issues is warranted. The advisory should also include some information about the carcinogenicity of styrene oxide, since it is a major metabolite and an active chemical which could relate to the possible carcinogenicity of styrene.

In the one-day Health Advisory, the data cited is from the article by Das and coworkers, not Srivastava and coworkers. Some explanation is also needed to justify using the study by Das in preference to that of Agarwal, which showed effects on dopamine receptors at 200 mg/kg/day.

ODW should extend the paragraph on the assessment of carcinogenic activity to provide a clearer explanation of why it chose this study and selected lung tumors for the evaluation. Because of the complexity of the data in this study, it is important for ODW to provide a more explicit description of how it used the data and factored early deaths with tumors into the estimate.

The last section concerns the possible biodegradation of styrene by oxidation. Since styrene oxide is a possible oxidation product and an active chemical, it should be considered here. Will styrene oxide be formed by this process? If so, what is the stability of styrene oxide in water, particularly at the range of pH of water coming from treatment plants. It is most important that the efforts to reduce the concentration of detectable styrene not be acheived by the generation of a different, but more active and more hazardous byproduct.

As noted in the discussion of n-hexane, styrene is a component of gasoline and some discussion of its presence as part of a mixture should be included.

A large number of typographical and editorial errors occur in the health advisory. For example, the melting point for styrene is -30.6 °C, while the value of 145°C is the boiling point. The density listed is incorrect. The statement about pulmonary absorption should be reworded to avoid the impression that the lungs were removed to measure retentions as might happen in studies of animals.

J. TOLUENE HEALTH ADVISORY

The toluene health advisory has a high level of typographical and editorial errors. For example, it incorrectly states the molecular formula. The reference dose calculation appears to have a hundred-fold error (stated as 28.8 mg/kg·day but calculated as 0.288 mg/kg·day). The health advisory states an LD_{50} for toluene that is ten-fold higher than that described in the Criteria Document.

The health advisory should refer to synonyms of methacide and methylbenzol.

The Office of Drinking Water should refer to the Agency's Health Assessment Document for Toluene for information on uses. The Criteria Document lacks any information on this subject, and the three uses cited in the health advisory, while correct, omit other significant uses. Similarly, the Criteria Document lacks information on occurence, while the health advisory does not cite the sources of information on occurence.

In the section on pharmacokinetics, the health advisory has correctly referred to information from the 1974 paper of Nomiyama and Nomiyama, but a numer of inconsistencies occur with the Criteria Document, which misquotes the data from this source.

The health advisory and the Criteria Document differ with respect to sources of toluene exposure. The health advisory refers to intentional abuse plus laboratory and occupational settings as the usual sources of exposure, whereas the Criteria Document cites drinking water, food, ambient air occupational settings and consumers products as sources of exposure to toluene.

The health advisory should briefly describe what is known about the mechanism of toxicity. The Subcommittee recommends that the health advisory provide a clearer statement of the human health effects of toluene. The health advisory refers to effects on the liver at 200 to 800 ppm, whereas the Criteria Document cites hematological effects associated with benzene contamination of toluene.

The data base is not up-to-date and should be compared against a standard reference data base.

K. XYLENES HEALTH ADVISORY (ORTHO-XYLENE, META-XYLENE AND PARA-XYLENE)

The health advisory for xylenes generally follows the Criteria Document for these compounds. The studies selected for establishing the known effects and for the calculations appear appropriate. For the health advisory on xylenes, the allowable exposures are based primarily on gross toxicity rather than the primary central nervous system effects. This may be necessary for the calculations, but the reader should be warned. The Subcommittee understands the difficulty created by the lack of oral administration data in the published literature.

While the health advisory correctly cites the amounts of xylene found in water, it does not recognize that other studies have occasionally found higher concentrations. An additional problem stems from the fact that values in the health advisory for the physical characteristics of the xylenes do not agree with those in the Criteria Document, notably the solubilities and the octanol/water partition coefficients. This appears to result from the use in the health advisory of an older version of the reference for these values (Verschueren).

A greater emphasis in the health advisory on metabolic profile studies actually conducted in humans would be more appropriate. These include work by Ogata, Riihiachi and Sedivec and Flek. The health advisory cites the latter in a different context. The health advisory may have used older references that are not adequately updated, but the Criteria Document has more recent data.

The health advisory may underestimate the possibility of effects on the liver. The studies by Tetrai and Ungvary cited in the Criteria Document suggest that this may be a sensitive target organ. The studies of Morley support this view, albeit in humans high levels of exposure were encountered. The epidemiological studies are equivocal. In this regard, EPA should consider the numerous studies on the capacity of these agents to induce drug metabolism.

The advisory acknowledges the study of Bowers and coworkers but dismisses it from consideration as the basis for the calculation. However, if material were lost by evaporation in this study, it would tend to underestimate the toxicity of the xylenes, not overestimate it. Furthermore, the lack of examination of other tissues is a moot point since positive effects were observed in the liver. The Criteria Document is not much help on this point since it tends to argue somewhat teleologically that the ultrastructural changes observed were adaptive in nature. However, one could also argue that the significance of these changes observed by electron but not by light microscopy is unknown.

The section on teratology is overly brief considering the number of available studies. The Criteria Document tends to emphasize that pregnant women may represent a sensitive population, but the health advisory does not address this issue fully. This lack of concern may be justified in view of the recent review of the complete literature commissioned by EPA, which reviewed the various studies from the perspective of dose and concluded that xylenes may be embryotoxic and maternally toxic but only at high doses.*

The study by Jenkins is hard to reconcile with that of Carpenter. In the Jenkins study, rats died at 3,358 mg/M^3, so it is difficult for the Subcommittee to accept Carpenter's no-observed-effect-levels of 2,000 and 3,500 mg/M^3.

The lack of a ten day health advisory conflicts with the position in the Criteria Document. Both the health advisory and the Criteria Document make the calculations using the same formula and data from the same study. Both documents arrive at the same values. However, the Criteria Document describes this calculation as a ten-day advisory, whereas the health advisory uses it as a long-term (not lifetime) advisory, which a water works official might use as a temporary ten-day advisory.

The calculations assume that 20% of human exposure to xylene arises from drinking water. This assumption is not supported by the data presented in the Criteria Document that demonstrates that only a very small amount (0.1 to 3.9 ug/kg/day) would be expected from air with essentially no intake from food. Thus, the inclusion of this factor is highly questionable.

The calculations of values for advisories should use the minute volume for the species from which the effect level is derived. Staff can then extrapolate the effect level for this species to humans.

Xylene is a component of gasoline and should be evaluated as part of this mixture, as discussed above in the comments on n-hexane.

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* R.D. HOOD and M.S. OTTLEY, "Developmental Effects Associated with Exposure to Xylene: A Review," Drug and Chemical Toxicology. 8: 281-297 (1985).

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Drinking Water Subcommittee
January 6-8, 1986

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COMMENTS SUBMITTED TO THE DRINKING WATER SUBCOMMITTEE

BY THE PUBLIC REGARDING THE SCIENCE ADVISORY BOARD'S

REVIEW OF DRAFT DRINKING WATER HEALTH ADVISORIES

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2501 M Street, N.W.
Washington, D.C. 20037

Date: December 26, 1986

Natural Resources Defense Council Inc. — Contact: Robin Whvatt, Wendy Gordan

122 East 42nd Street
New York, N.Y. 10168

Date: November 29, 1986

Water Quality Association — Contact: Danna M. Cirolia

1518 K Street, N.W.
Suite 401
Washington, D.C. 20005

Date: November 22, 1985

Diamond Shamrock Corporation — Contact: Ross E. Jones

World Headquarters
717 North Harwood Street
Dallas, Texas 75201

Date: December 2, 1985

American Cyanamid Company
One Cyanamid Plaza
Wayne, New Jersey 07470

Contact: Linda Dulak

Date: November 27, 1985

The Society of the Plastics Industry, Inc.
1025 Connecticut Ave.
Washington, D.C. 20036

Contact: Hugh Toner

Date: December 16, 1985

The New Jersey Dept. of Health and The New Jersey Dept. of Environmental Protection

Contact Bonnie L. Bishop

August, 1984

State of Connecticut
Department f Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council
Educational, Non-Profit
Non-Political thru Investigation, Research

Contact: Martha Johnson

December 12, 1985

Synthetic Organic Chemical Manufacturers Assn.
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Alan W. Rautio

November 27, 1985

Ethylbenzene Producers' Association
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Eric A. Clark

November 27, 1985

Synthetic Organic Chemical Manufacturers Association
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Alan W. Rautio

December 18, 1985

POST MEETING COMMENTS RECEIVED

National Audubon Society
National Capital Office
645 Pennsylvania Avenue, S. E.
Washington, D. C. 20003

Contact: Chuck Pace

Date: January 27, 1986

Hazco
5301 Lee Highway
Arlington, Virginia 22207

Contact: Redmond Clark

Date: March 14, 1986

Chemical Manufacturers
Association
2501 M Street, N. W.
Washington, D. C. 20037

Contact: Ann M. Mason

Date: April 30, 1986

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Drinking Water Subcommittee

Open Meeting

Under Public Law 92-463, notice is hereby given that a three-day meeting of the Drinking Water Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 6-8, 1986, in Conference Room 451 of the Joseph Henry Building; National Academy of Sciences; 2122 Pennsylvania Avenue, N.W.; Washington, DC. 20037. The meeting will start at 9:00 a.m. on January 6 and adjourn no later than 4:00 p.m. on January 8.

The purpose of the meeting will be to discuss draft drinking water Health Advisory documents for the following substances:

Acrylamide	Legionella
Benzene	Methylethylketone
p-Dioxane	Styrene
Ethylbenzene	Toluene
Ethylene glycol	Xylene
Hexane	

The Drinking Water Subcommittee will not receive oral comments on the Health Advisory documents at the meeting. Written comments on any of the specific substances should be delivered within forty (40) days from the date of this notice to Manager, Health Advisory Program; Criteria and Standards Division [WH-550]; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460.

EPA's Office of Drinking Water prepared the draft Health Advisory documents. They are neither regulations nor regulatory support. To obtain copies of the draft Health Advisory documents for specific substances please write to the Manager of the Health Advisory Program at the above address.

The meeting will be open to the public. Any member of the public wishing to attend or to obtain further information should contact either Dr. Daniel Byrd, Executive Secretary to the Committee, or Mrs. Brenda Johnson, by telephone at (202)382-2552 or by mail to: Science Advisory Board (A-101F); 401 M Street, S.W.; Washington, DC; 20460, no later than c.o.b. on December 20, 1985.

Terry F. Yosie
Staff Director
Science Advisory Board

October 15, 1985

Date

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE
DRINKING WATER SUBCOMMITTEE

Conference Room 451
Joseph Henry Building
National Academy of Sciences
2122 Pennsylvania Avenue, NW
Washington, DC 20037
January 6-8, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

Opening Remarks	.....	Dr. Tardiff
Administrative Matters	.....	Dr. Byrd
Introduction	.....	Dr. Crisp Dr. Tardiff

*Tentative Sequence of Reviews, beginning Monday, January 6, 1986

Substance (Manager)		Reviewers
p-Dioxane (Khanna)		Drs. Johnson and Ray
Ethylbenzene (Khanna)	.....	Drs. Andrews and Ray
Ethylene glycol (Khanna)		Drs. Ray and Johnson
Toluene (Khanna)	.....	Drs. Griffin and Dajirmanjian
Benzene (Marcus)		Drs. Brubaker and Kim
Styrene (Marcus)	.....	Drs. Kaufman and Andrews
Xylene (Patel)		Drs. Carlson and Griffin
Methylethylketone (Patel)	.....	Drs. Tephly and Brubaker

On Tuesday, January 7, 1986

Legionella (Berger)	.....	Drs. Barbaree and Winn

On Wednesday, January 8, 1986

Acrylamide (Crisp)		Drs. Dajirmanjian and Weiss
Hexane (Patel)	.....	Drs. Kim and Tephly

At the conclusion of the reviews

*Completion of reviews (previously deferred)	Dr. Tardiff
General comments	Dr. Tardiff
Nomination of Criteria Documents for further review	Dr. Tardiff

Other Subcommittee Business

Concluding remarks	.....	Dr. Tardiff Dr. Byrd

ADJOURNMENT

* The sequence in which the Subcommittee reviews Health Advisories for different substances and the time allocated to each review are at the discretion of the Chair.